OBSERVATIONAL STUDY OF MEDULLOBLASTOMA, BARNARD INSTITUTE OF RADIATION ONCOLOGY, MADRAS MEDICAL COLLEGE, CHENNAI- 2001 – 2010

Dissertation submitted in partial fulfilment of the requirements for the degree

DOCTOR OF MEDICINE
RADIOTHERAPY
MD BRANCH-IX

DEPARTMENT OF RADIOTHERAPY
MADRAS MEDICAL COLLEGE
&
RAJIV GANDHI GOVERNMENT GENERAL HOSPITAL
CHENNAI-600 003

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI.

2016 - 2019

CERTIFICATE

This is to certify that **Dr. T.BHARATHI** has been a postgraduate student during the period May 2016 to May 2019 in the Department of Radiotherapy, Madras Medical College and Rajiv Gandhi Govt. General Hospital, Chennai.

This Dissertation titled **"OBSERVATIONAL STUDY OF MEDULLOBLASTOMA IN BARNARD INSTITUTE OF RADIATION ONCOLOGY 2001-2010"** is a bona fide work done by her during the study period and is being submitted to the Tamil Nadu Dr. M.G.R. Medical University in partial fulfilment of M.D. Branch-IX Radiotherapy Examination.

Prof. Dr. R.JAYANTHI, M.D, F.R.C.P.
Dean
Madras Medical College &
Rajiv Gandhi Government General Hospital,
Chennai-600 003.

DECLARATION

I solemnly declare that the dissertation titled **"OBSERVATIONAL STUDY OF MEDULLOBLASTOMA IN BARNARD INSTITUTE OF RADIATION ONCOLOGY 2001-2010",** a retrospective study was done by me at the Department of Radiotherapy, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai for a period of 1 year under the guidance and supervision of **Prof. Dr. R.GIRIDHARAN, M.D.RT.** The Dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfilment for the award of M.D. Degree (Branch IX) in Radiotherapy.

Dr. T.BHARATHI
M.D. Radiotherapy Post Graduate Student
Department of Radiotherapy.

Place: Chennai
Date:

ACKNOWLEDGEMENT

I express my profound gratitude to **Prof. Dr. R.JAYANTHI, M.D, F.R.C.P, Dean**, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai, who with his vast knowledge and experience has been a great source of inspiration. I am grateful to him for enabling me to utilize the facilities of this institution for conducting this study.

I express my sincere gratitude to **Prof. Dr. SUDHA SESHAIYAN, M.D.,** Vice Principal, Madras Medical College, Chennai for her kind words of encouragement.

I express my gratitude to Chairman **Dr. C. RAJENDRAN M.D.,** and the members of the Ethical Committee Council of Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai -03, affiliated to The Tamil Nadu Dr.M.G.R Medical University, Chennai -32 for having approved my study and for his valuable suggestions.

I am extremely grateful to **Prof. Dr. N.V. KALAIYARASI, M.D.R.T., D.C.H.,** Professor & Head, Department of Radiation Oncology, Rajiv Gandhi Government General Hospital, Chennai, for having devised the study, for her periodic monitoring, intellectual input, kind encouragement and support throughout the study and the prompt help rendered whenever approached.

I am extremely thankful to **Prof. Dr. R. GIRIDHARAN, M.D.R.T., D.M.R.D.,** for his guidance, encouragement and help rendered throughout my study. 6

I am grateful to **Prof. Dr. VISHWANATHAN, M.D,** Head – Department of Radiation Oncology, IOG, Egmore who helped me with his timely advice during this study.

I wish to express my sincere thanks to all the former and present Assistant Professors of our department for helping me with their timely advice during this study.

Dr. BASKAR, M.D.R.T, D.M.R.T.,

Dr. MADHUMATHI, M.D.R.T, D.M.R.T.,

Dr. SUNDARESAN, M.D.R.T.,

Dr. SANJAL, M.D.R.T.,

Dr. VIJEY KARTHIK, M.D.R.T.,

Dr. POONGODI, M.D.R.T.,

Dr. JEYASHANKER, M.D.R.T.,

Dr. SENTHILKUMARAN, M.D.R.T.

I am also indebted to the Radiation Physicists of our department **Prof.Dr.MUTHUVELU & Mrs.A.KOPPERUNDEVI,** for giving me their valuable time and help. I also wish to thank all the paramedical personnel and post graduates of our department for their co-operation which enormously helped me in this study.

I am grateful to **Prof.Dr.JAGDISH CHANDRA BOSE, M.S., M.Ch.,** former Professor and Head, Department of Surgical Oncology, and **Prof.Dr.K.KALAICHELVI, M.D., D.M.,** Professor and Head, Department of Medical Oncology, for their prompt help rendered whenever approached.

Last but not the least I wish to acknowledge the support of my family members and the co-operation of my patients and the blessings of the Almighty without which this work would have been highly impossible.

CONTENTS

INTRODUCTION

Medulloblastoma is the most common malignant brain tumor of childhood with an annual incidence of about 0.5-0.8 / 1,00,000 in children, younger than 19 years of age(1) (22) . It is relatively less common in adults. The incidence in adult is 0.5 per 100,000. (11) It is the second most common type of pediatric brain tumors (16). (Low grade gliomas are the first commonest pediatric brain tumors, which constitutes 35-50%). It is a highly invasive, malignant embryonic tumor. Historically, it has been classified as a primitive neuroectodermal tumors (PNETs), but now, it is no longer considered as a PNET entity. It is a member of small blue round cell tumors. Mostly it occupies the posterior fossa, or cerebellum. (15).

It constitutes about 40% of all posterior fossa tumors. The other tumors of posterior fossa are ependymoma, astrocytoma, brainstem glioma and metastases (34). Currently medulloblastomas are thought to arise from cerebellar stem cells that have been prevented from dividing and differentiating into their normal cell types.

Medulloblastoma is seen like filled with small ovoid cells, which have a darkly stained hyper chromatic nuclei and frequent mitoses. Other members of small blue round cell tumors are Ewing's sarcoma , Rhabdomyosarcoma, Synovial sarcoma,

Hepatoblastoma, Neuroblastoma, Retinoblastoma, and Non-Hodgkin's lymphoma(31) . Both periventricular pseudo rosettes and Homer Wright rosettes (clustered cells surrounding central eosinophilic core) are highly characteristic of medulloblastoma and seen in half of the cases. It is told that the cancer stem cells are present in the perivascular niche.

The commonest age group affected in adult is 20-40 years, (16) and it is mostly eccentrically placed in posterior fossa (50%). Adult medulloblastoma are frequently desmoplastic variant, and the presence of severe anaplasia is also **less** in adult medulloblastoma. In children it accounts for 3% of total pediatric cancers and 10-20% of brain tumors.It is mostly centrally placed tumor in cerebellar region and floor of 4th ventricle , adverse prognostic factors include 1)male gender and 2) age less than 3 years. Patients with surgical excision of tumor either near- totally or totally, fare better than those with partial excision or biopsy only.

The male : female ratio worldwide is **2:1**.The incidence of medulloblastoma is higher in males and higher in early childhood(16), (22), almost half of the cases occur before age of 5 (34).Established prognostic variables accepted by North American Children Oncology Group (COG) and the SIOP (international society of pediatric

oncology) group : Patients are classified as *average risk and high risk* groups.

If the age is > 3 years ,if patient has < 1.5 cm2 (maximum cross sectional area) of residual tumor and no dissemination it is considered as standard risk category.

If patients with age > 3 years, > 1.5 cm2 of residual tumor and/ or evidence of CSF dissemination or < 3 years of age at diagnosis,they are considered as high risk. Children less than 3 yr of age , hemispheric location, high risk according to risk stratification, and patients who do not receive radiation therapy affected the prognosis- in univariate analysis. In multivariate analysis, hemispheric location and high risk influenced death.(3)

Syndromes associated with medulloblastoma are Gorlin Syndrome (18), (19), (38) and Turcots Syndrome (18). Gorlin syndrome is also known as *nevoid basal cell carcinoma syndrome,/ gorlin - goltz syndrome* .It is an inherited condition with multiple body systems involvement such as multiple basal cell carcinoma, in face ,arm, and trunk(skin), microcephaly, medulloblastoma (nervous system), ovarian fibroids (endocrine system) and frontal bossing, bony cysts, kyphoscoliosis, bifid ribs and small metacarpals bones (38). Risk of death in Gorlin syndrome due to medulloblastoma is 50% if the age is less than 4 years.

Turcot syndrome is characterized by multiple adenomatous colonic polyps with an increased risk of colorectal cancers, and brain tumors (19). CSF dissemination may manifest as positive cytology or macroscopic seeding of the sub arachnoid space .It is not a common manifestation . Only 30-40% of cases present with CSF spread at the time of presentation and diagnosis. Systemic spread is mostly to bone and bone marrow (15). This pattern of spread is considered in the analysis of dissemination in CHANG staging.

Medulloblastoma is clinically classified by Chang et al in 1969 based on size and invasiveness of tumor as determined intra operatively and on the presence of metastases. But, Chang staging is no longer used now, although elements from it form current clinical risk stratification. Chang staging is helpful to differentiate standard risk patients and high risk patients. M0 is without any metastases anywhere. M1 stage is presence of tumor cells in cerebrospinal fluid (CSF). It can be seen in MRI or by CSF cytology. M2 is having gross nodular seeding in cerebellar sub arachnoid space, cerebral subarachnoid space, third ventricle and fourth ventricle, i.e. other than the primary site intra cranially. M3 stage consists of gross nodular seeding in spinal subarachnoid space. M4 is extra neural metastasis.

The world health organization (WHO) (34) pathological classification of brain tumors includes 5 subtypes of medulloblastoma.

Histologic subgrouping includes classic, desmoplastic, large cell, anaplastic and medulloblastoma with extensive nodularity variety.

Classic medulloblastoma constitutes the commonest histology (66%), and it is composed of sheets of closely packed small blue round cell with a high nuclear to cytoplasmic ratio, mitotic and apoptotic activity. It may occur mostly in midline.

Desmoplastic and nodular varieties constitute 15% of total occurrence . Desmoplastic variety carries a favorable prognosis, and it may arise laterally in cerebellar hemispheres. This variety compromise small blue round tumor cells typically harbor reticulin rich stroma with reticulin free pale islands, which are immune positive for **synaptophysin** indicating neuronal differentiation. Cells show **glial fibrillary acidic protein** immunopositivity.

Recently a consensus **conference in Boston in 2010** supported classification of 4 main subgroups of medulloblastoma on the basis of molecular genetics. Integrated genomic studies revealed medulloblastoma into 4 distinct molecular and clinical variants, termed WNT/ (beta Catenin), SONIC HEDGEHOG, GROUP 3 AND GROUP 4 (33). The Wnt and Shh groups are named after the predominant signaling pathways thought to be affected. Cytogenetic abnormalities found are loss of 17p, amplification of MYC-C, and amplification of MYC-N. As advances in the molecular and genetic

profiling of pediatric medulloblastoma evolve, associations with prognosis and treatment are found. (34) It is noted as mentioned below:

WNT subgroup of medulloblastoma arises from lower rhombic lip of 4^{th} ventricle especially from mossy neuron fiber precursors. It carries a very good long term prognosis (90%). It is the rarest molecular type. The Wnt pathway inhibitor APC gene predispose to turcots syndrome. (19). Wingless is a family of growth factor receptors that are involved in embryogenesis and in "cell to cell" control mechanism. The histology of this subgroup is usually Classic histology, which is positive for IHC- beta catenin staining, CTNNB1 mutation which encodes for beta catenin and PTCH mutation. It is associated with loss of chromosome 6 and rarely expresses chromosome 17 aberrations.

Sonic hedgehog subgroups accounts for 28% of all medulloblastomas. It arises from external granular layer of cerebellum. It can be identified by transcriptional profiling, IHC staining for SFRP1. It is of interest because of the availability and temporary success of (SMO)small molecular inhibitors. The subgroups frequency is less between 3-16 years of age group. Nodular / desmoplastic histology is present. Aberrant SHH signaling in normal human development may cause holoprosencephaly. SHH ligand is normally secreted by purkinji neurons. Prognosis is "in between" WNT (good) and group 3 (poor).

Group 3 or Group C subgroup mostly has the histology of classic medulloblastoma. It has a male preponderance than for females. One peculiar issue is it is almost never observed in adults. It is notorious for frequently metastatic, recurrence and death occurrence. It carries a poor prognosis due to be presence of MYC amplification. It is the more specific point in prognosis.

Group 4 or Group D subgroup is most common typical group of medulloblastoma. In frequency of occurrence it is accounting for 34% .The peak age of occurrence is 10 years. It is considered as prototypical medulloblastoma. KCNA1 is an IHC marker of group 4 variety. It has tendency to have is chromosome 17 q and Loss of X chromosome.

It's aggressive pattern of growth , it's tendency of lepto meningeal spread and drop metastasis in cauda equine regions, create the need for intensive combined modality therapy. The survival rates depend upon age groups and histology, which is 60%, 52%, and 47% at 5 years, 10 years and 20 years respectively.

In treatment aspect , all the localized tumors must be excised with maximum safe resection, no margins are needed because knife is not supposed to be put in normal brain. Sometimes, brainstem involvement may present, which stops from complete resection. In surgical treatment method, patients have to undergo ventriculo -

peritoneal shunt and excision of intracranial tumor. Near total excision or total excision of the intracranial tumor is preferred than the subtotal excision. When there is an obstruction to flow of CSF due to the presence of tumor, patients need to undergo ventricular peritoneal shunt. When obstruction is removed, the increased intra cranial tension is relieved. Patient gets relieved from headache, vomiting and blurring of vision after this surgery.

Posterior fossa syndromes(40) is the development of collection of neurological symptoms like dysphagia, trancal ataxia, hypotonia , mutism, respiratory failure, cranial nerve deficits, neurobehavioral changes and urinary retention or incontinence after posterior fossa craniotomy for medulloblastoma tumor excision. It is also called "cerebellar mutism" It occurs in 10-15% of children after posterior fossa resection.

Post-operative radiotherapy should begin within 28-30 days after resection, whenever it is possible. Radiation should be given to whole of spine and cranial fields. It must be followed by a *boost* of radiation to full of posterior fossa of brain, using opposing lateral fields. Multiple fields can also be used to spare cochlea.

We can go for simple opposing posterior obliques for posterior fossa. Adults can be given radiation to cranio-spinal fields up to 36 Gy, because of the lesser incidence of neural and cognitive impairment in

adults (25). Comparatively, children are prone for more long term complications of nervous system like irritability, growth defects, delay in secondary sexual characters development (7), etc. Pediatric cases can be treated with 23.4 Gy cranio-spinal irradiation (13), as long as appropriate chemotherapy is given along with it.

The total dose to posterior fossa must be 45-50 Gy for spinal metastatic conditions and it can be proceeded up to 50-54 Gy in case of intra cranial metastases. Treatment daily dosage is 1.8 Gy single fractions. Radiation to cribriform plate region is also important to prevent recurrence. (41). It is told P13 K pathway regulates the survival of cancer stem cells, residing in perivascular niche following radiation in medulloblastoma in vivo(42).Posterior fossa boost can be done better with 3DCRT and planning is done with CT/ MRI. It is said hyper fractionation reduces the delayed complications.Non CNS tumors can occur in ares which received radiation. Gliomas can occur.

Adult patient's tolerance for chemo is very poor. PCV regimen is one which is widely used along with weekly inj.vincristine 1.4mg /m2. Targeting with agents like cyclopamine (35) vismodegib (36) (GDC-0449) and saridegib(37) were being given.

As a general rule, adult patients also must be treated with same treatment modality like pediatric patients, but poor tolerance is encountered at many times during

treatment with weekly inj. Vincristine. Also the role of chemotherapy in adult is not yet proven clearly, as it was proven in pediatric cases. The 10-year over all survival reported was 53% and the 10-year progression-free survival was 40%.

The occurrence of complications may be seen in a spectrum of expressions.

It can be acute or long term. Pubertal delay (7) is one of the common complications, intellectual incompetence also often encountered as a long term complication (6). Half of patients required a long-term thyroid hormone supplementation. Growth hormone administration may be needed. Often sex hormone replacement may be needed in many patients. Deficiency of ACTH and diabetes insipidus were seen in very few of the patients. Older patients show a delay in declination of performance, younger children show immediate loss of performance(6)

At the time of follow-up, one third of patients may have short stature with $< 3^{rd}$ percentile. Few patients have obesity, their body mass index will be $> 97^{th}$ percentile. Patients had reported with significant

alopecia, mainly seen in occipital region of scalp. Mainly because of their alopecia, patients were highly dissatisfied with their physical appearance . It is important to minimize the treatment related toxicity (9).

Nearly half of the patients reported about significant perioperative neurological complications that persisted during long-term survival follow-up.These complications included facial nerve palsy, strabismus, hearing impairment and visual impairment, hemiparesis and tetra paresis. Almost all patients had significant neurocognitive mal functioning: Attention impairment and delay in processing speed , learning impairment and memory impairments were present in some patients.

Language impairments, visual perception impairments and executive function impairments also present in patients. Significant impairments in overall level of the intellectual functioning (IQ < 85) was seen in many patients. In patients who did not receive any radiotherapy, language impairment is present, but the overall level of intellectual functioning in them was normal. Patient experienced significant problems in school.Many of the patients are studying in special school. Few patients do attend regular schools, but they need remedial teaching.

Several patients complained about their inability to concentrate and about difficulties with comprehension and delayed speed of working. Among patients of employable age, very few are able to follow a professional training in specialized institution, half of them are unemployed at the time of survey. Many of the patients were not able to take up their preferred job because they were unable to obtain the required qualifications. Their friendships mainly turned out to be not very strong and many survivors do not have any friends at all. Patients reported difficulties in making friends. While the grave prognosis associated with medulloblastoma is fully justifiable, it appears that some hope can be given to parents, since practically 40 % of our cases completing treatment have survived 5 years , and 30% , 10 years.(8).

REVIEW OF LITERATURE

1.Outcome of Medulloblastoma in Children: Long-Term Complications and Quality of Life Article Neuropediatrics June 2006 ,This study reveals some important aspects like

- The mean follow-up time of all 51 patients following primary surgery was 6.6 years (range: 0.1 to 24.0 years). The 10-year overall survival was 53% and the 10-year progression-free survival was 40% as determined by the Kaplan-Meier method [26];
- 44% patients had short stature.
- Facial nerve palsy (n = 4), strabismus (n = 2), hearing impairment (n = 3), visual impairment (n = 2), hemi-and tetraparesis (n = 3),
- Thirteen (72%) patients experienced significant problems in school.

2.Treatment of early childhood medulloblastoma by postoperative chemotherapy and deferred radiotherapy Stefan Rutkowski, Nicolas Ulrich Gerber,for the German Pediatric Brain Tumor group *(S.R., N.U.G.,*1.After identifying the detrimental effects of craniospinal irradiation on the neurocognitive outcome,2,5–9,21,32,33 different strategies aiming to avoid craniospinal radiotherapy have been

developed by different study groups.2. desmo -plastic histological subtypes were newly identified as an independent favorable prognostic factor3. cyclophosphamide, carboplatin, and vincristine were included.

3.Survival and prognostic factors in pediatric patients with medulloblastoma in southern Thailand, Nalita N et al. J pediatr neurosci 2018 apr – jun Children less than 3 yr of age , hemispheric location, high risk according to risk stratification, and patients who do not receive radiation therapy affected the prognosis- in univariate analysis. In multivariate analysis, hemispheric location and high risk influenced death.

4.Survival of patients with adult medulloblastoma : A population based study Rose Lai et al. cancer 112 (7) , 1568-1574, 2008. Says adult medulloblastoma constitutes less than 1 %.

5.Survival and secondary tumors in children with medulloblastoma receiving radiotherapy and adjuvant chemotherapy : results of children s oncology group trial A 9961, Roger j packer, Tianni Zhou, Emi holmes, Neuro oncology 15 (1), 97-103, 2012. Shows 5 yr survival rate – 82 %, 10 yr survival 75 %, 15 /377 patient developed secondary tumor, after 5 yr of diagnosis. Non CNS solid tumors occur in areas which received radiation. Gliomas can occur.

6. Predicting intellectual outcomes among children treated with 35- 40 Gy craniospinal irradiation for medulloblastoma, SL Palmer, A Gajjar, WE Reddick...2003- psychonet .apa.org to trend the childrens intellectual performance as a function of time since diagnosis, older patients show a delay in declining of performance, younger children show immediate loss of performance with plateau at approximately 6 years post diagnosis.

7.Effect of hypothalamic and pituitary irradiation on pubertal development in children with cranial tumors, RRappaport , R Brauner, P Czernichow, The journal of clinical endocrinology & metabolism 54 (6), 1164- 1168, 1982 to report on gonadotrophin function and puberty of a large group of children treated with craniospinal irradiation.1/3 of children didn't have pubertal development. GH deficiency associated with gonadotrophin deficiency as a consequence of 60 rads of RT.

8.The treatment and prognosis of medulloblastoma in children, a study of 82 verified cases, H.J.G BLOOM, WALLACE and J M HENK jan 1969, Although widespread intrathecal tumor is generally present in fatal cases, the chief cause for therapeutic failure is persistence or recurrence at the primary site. While the grave prognosis associated with medulloblastoma is fully justifiable, it appears that some

hope can be given to parents, since practically 40 % of our cases completing treatment have survived 5 years , and 30% , 10 years.

9.Survival in padiatric medulloblastoma : a population based observational study to improve prognostication. Weil et al, Neuro Oncol,2017 the probability of mortality from a neurological cause is < 5% if the patient survives 8 year after diagnosis. Majority of them survive in modern era. So the importance of minimizing the treatment related toxicity is increasingly apparent given the likelihood of long term survival.

10.A prospective study of progregression free and overall survival in pediatric medulloblastoma based on molecular subgroup classification. A single institutional study. Tao jiang et al, yugi zhang,jummei wang, jiang du,may 2017. Non metastasized Group 4 patients has an excellent prognosis (2 yr OS-09.6%), the SHH subgroup and group 3 have worst prognosis. Large cell / anaplastic histology had a dismal prognosis, which warrants intensive treatment.

11. Incidence and survival trends for medulloblastoma in united states from 2001-2013. Khanna V et al. J Neuro oncol. 2017..incidence was highest in patients aged 1-4 years at diagnosis, but patients aged 10-14 years showed increased incidence durig the year 2001- 2013.male showed increased incidence from 2000 to 2013.

12.Survival following tumor recurrence in children with medulloblastoma, D L Johnson et al. 2018 the OS at 1 year was 83.6%, 3 years- 77.9%, at 5 years 72.2%. progression free survival- 1 year- 78%, 3 years- 70% and in 5 years- 69%. 31% have recurrence. recurrent medulloblastoma in pediatric age gives a poor prognosis, there is a need for novel treatment approaches for this group.

13.Survival of very young children with medulloblastoma with treated with craniospinal irradiation , saran F H et al.Int Radiat oncol Biol phys. 1998 very young children have worst prognosis than older children. Inadequate radiation dose and technique to the primary tumor region may be a contributing factor. Concurrent chemotherapeutic regimens alone are not sufficient to compensate for reduced radiation doses and volumes.

14.Medulloblastoma : recurrence and metastasis, Donya Aref; Sidney Croul, CNS Oncology , 2(4) 377-385, jul 2013 although there is now long term survival or cure for majority of patients, the survivor bears a significant burden of complication, due to intense therapies given to ensure eradication of tumor. It is now important to distinguish between patients who do and do not need intensive therapy, by clinical risk stratification, pathological diagnosis and genetics, genome studies.

15.Impact of site of tumor recurrence upon survival for children with recurrent or progressive medulloblastoma, Bowers DC

et al, J Neuro surg . 2007 cox variant analysis showed showed a significant association between prolonged survival and only one Variable- tumor recurrence restricted to site of primary. There is no significant association between other variables like sex, age, interval from diagnosis and progression, initial tumor stage and salvage treatment with chemotherapy.

16. Incidence of medulloblastoma in Canadian children, Johnson DL et al. J Neuro oncol. 2014 there is a male predominance.. the incidence rate is double in case of age less than 5 years patients. Male incidence show ups and downs but female incidence is stable.

17. Incidence of Gorlin syndrome in 173 consecutive cases of medulloblastoma, Evans DG , et al, Br J Cancer 1991 incidence of medulloblastoma in Gorlin syndrome is 3-5%. Risk of 50% death in Gorlin syndrome due to medulloblastoma in age less than 4 years .

18. A gene for nevoid basal cell carcinoma syndrome acts as a tumor suppressor gene in medulloblastoma, Cowan R et al, 1997patient with Gorlin syndrome will develop medulloblastoma in the first few years of life. Majority Gorlin syndrome patient have loss of wild type allele on 9 q, indicating that the Gorlin locus probably acts as a tumor suppressor gene in the development of medulloblastoma.

19. Congenital anomalies and genetic syndromes in 173 cases of medulloblastoma, Evans G et al. Med Pediatric Oncol. 1993 a previously un reported association with Rubinstein Taybi syndrome was found.

20.Congenital icthyosis and medulloblastoma Walach N Dermatologica. 1977 together occurence a is very rare. but presented in 18 yr female.

21. Medulloblastoma in children and adolescents: a systemic reiew of contemporary phase 1 and 2 clinical trial and biological update. Francisco baustica, victoria fioavantti et al, 2017 nov 6(11)newer targeted agents are in phase 1 and 2 studies. Temozolamide containing regimen had median survival of 16.5% smoothened inhibitor trials had median ORR of 8%.temozolamide is the backbone of newer chemo regimens

22. Medulloblastoma in childhood: an epidemiological study, farwell JR et al J Nuerosurg 1984. A relationship between polio vaccine infected with SV40 virus and medulloblastoma development. Children with medulloblastoma have increased number of family members with brain tumors , leukemia or childhood cancers.

23.Quality of life for survivors children irradiated for brain tumor before the age of 4 years: jenkin et al . med pediatric oncol

1998 10 year survival rate was 40%,. 54 % of survivors didn't harbor any major neurological, visual or hearing defects. Among adult survivors, older than 21 yrs, have complted higher education 26%. 31 % were in full time employment. 37% hadnever employed. Search for a less toxic treatment is appropriate.

24.Quality of long term survival in young children with medulloblastoma, jonson et al. J Nuerosurg 1994 23 families were interviewed by telephone among them 13 came to hospital, I Q was less than 90% for all participants,pt who undergone shunting had more test scores in reading, spelling and mathematics. Perceptual motor task performance were poor in 50% of participants. Problem in learning and delay in physical growth anddevelopment seen in majority of patients.

25. Brandes et al, long term results of prospective phase 2 trial of adult medulloblastoma: treated with neoadjuvant chemotherapy 2 cycles followed by radiation and followed by chemotherapy again. median followup of 7.6 years, 5 year overall survival rate 75% , (for high risk patients – 73% and average risk patients- 80%) and progression free survival rate 72% (for high risk patients 69%. For average risk patients- 80%)

26.Duffner et al. (1993) : assessed whether RT can be delayed by giving chemo post operatively and delay in RT until > 3 years age. Chemo given was 2 cycles of cyclophosphamide and vincristine

followed by 1 cycle of cisplatin and etoposide. RT given was CSI 35.2 gy and posterior fossa dose 54 gy. Study saysit is safe to delay RT until the age > 3 years.

27.P9934 trial : combination chemotherapy followed by second look surgery and radiation therapy in treating children with nonmetastatic medulloblastoma or primitive neuro ectodermal tumors, august 2013 – children oncology group- to determine the treatment for 8 months to 3 years of age group. It allows feasibility of telephone interview of patients based on data collection method for neuropsychological evaluation.(drugs used cisplatin, cyclophosphamide and etoposide)

28. COG ACN 0331 trial :Children oncology group- involved field RT and low dose craniospinal irradiation with chemotherapy in average risk medulloblastoma, says , survival rates of reduced RT boost volumes were comparable to standard treatment volume for the primary site of tumor. There is no survival difference between both techniques. Reduced dose to craniospinal axis associated with higher event rates and worst survival.

29.ACNS 0334 trial :for the treatment of newly diagnosed supratentoreal PNETs and high risk medulloblasoma children more than 3 years of age intensive induction chemotherapy with methotrexate followed by consolidation stem cell rescue

30. neuropsychological sequel of the treatment of children with medulloblastoma , july 1996, Maureen dennis, Brenda j.spiegler, c.ross Hetherington : survivors have long term deficits in intelligence, memory, language, attention, academic skills, psychological function, and a compromised quality of life. Age at diagnosis and time since treatment are important contributors of intellectual morbidity. These children progressively fail to assimiliate new verbally based knowledge at a developmentally appropriate rate.

31. the perceived impact of cancer on quality of life for post treatment survivors of childhood cancer, brad j zebrack, wendy landier, march 11, 2011 – says quality of life and distress are partially a function of survivors perception of how cancer has affected them and continues to affect them both in positive and in negative ways.

32.http: // www.ncbi.nlm.nih.gov/pmc/articles/ PMC3167982/ **small blue round cell tumors**.j am Podiatr Med Assoc. 2011 jul-aug ; 363-9, small blue round cell tumors.

33.**Molecular classification of medulloblastoma**: Sarah ES Leary.2012 james m oslan,, journal of clinical oncology, official journal of American Society of clinical oncology 2011; 29_ 1424-1430.

34.Pediatric medulloblastoma- update in molecular classification driving targeted therapies- ruth-mary desouza,benjemin R.T.jones front oncol 2014,4: 176, july 22 2014.

35.Thyroid dysfunction as a late complication of childhood medulloblastoma : a comparision between hyper fractionated RT vs conventional RT, Umberto ricordi, andre corries,silvia finaudi, international journal on radiation oncology* biology* physics 50 (5),1287-1924.2001: hyperfractionation can reduce the delayed effects of radiation injury.

AIMS AND OBJECTIVES

This study is conducted to evaluate the medulloblastoma patients who attended the treatment in department of radiation oncology , madras medical college , chennai, during the period january 2000 to December 2010 in respect to agewise and genderwise distribution, tumor site wise and histological subtype of tumor wise survival analysis , treatment modalities undergone and their survival rates .

AIM OF THE STUDY

- To study the long term outcome of medulloblastoma patients, who were treated in our institution during the period 2000-2010
- It is a retrospective study with available clinical record and patients follow up
- Outcome analysis was done with respect to
  - Age and sex distribution
  - Tumor location
  - Clinical presentation
  - Treatment modalities
  - The response to treatment

MATERIALS AND METHODS

DISCLOSURE: This study was done purely in the government hospital after obtaining the consent from individual patients. The Tamil consent form is attached. The Ethical committee clearance was obtained prior to this study. The study was often reviewed and presented periodically in the department during the course.

Estimation of sample size: sample size could not be predicted by significance levels and error estimations. It is done with total coverage of 10 year period from 2000 to 2010. All the patients were included and the total number becomes the sample size.

CRITERIA FOR INCLUSION IN STUDY

We include three criterias of inclusion,

- All cases must be a **biopsy proven** medulloblastoma patients.
- They should **be registered** in department of radiation Oncology, RGGGH,Chennai
- The treatment period should be between **January 2000-December 2010**.

CRITERIA FOR EXCLUSION IN STUDY

- Patients without HPE documentation

- Patients who undergone treatment at other institutions.

DATA COLLECTION

Year	Cases of nervous system	Madulloblastoma cases
2001	127	7
2002	98	7
2003	139	8
2004	123	3
2005	111	10
2006	89	3
2007	88	5
2008	128	12
2009	124	8
2010	99	9

Case records of medulloblastoma patients who were treated during the period 2000 - 2010 were collected from MRD. Totally 18,213 case sheets were analyzed during the study period and 75 patients of medulloblastoma were included for the study.

Majority of them were lost for follow up. During that treatment period (2000-2010), mobile phone facility was very much limited. Some patients had given partial addresses only, so we were not able to trace their address. Permission obtained from all the three

oncological department, (medical oncology , surgical oncology and radiation oncology) and pooled data of these patients were arrived. With the help of NGOs, village health nurse surveillance, volunteers 75 patients location and survival status were known, within 6 months period.

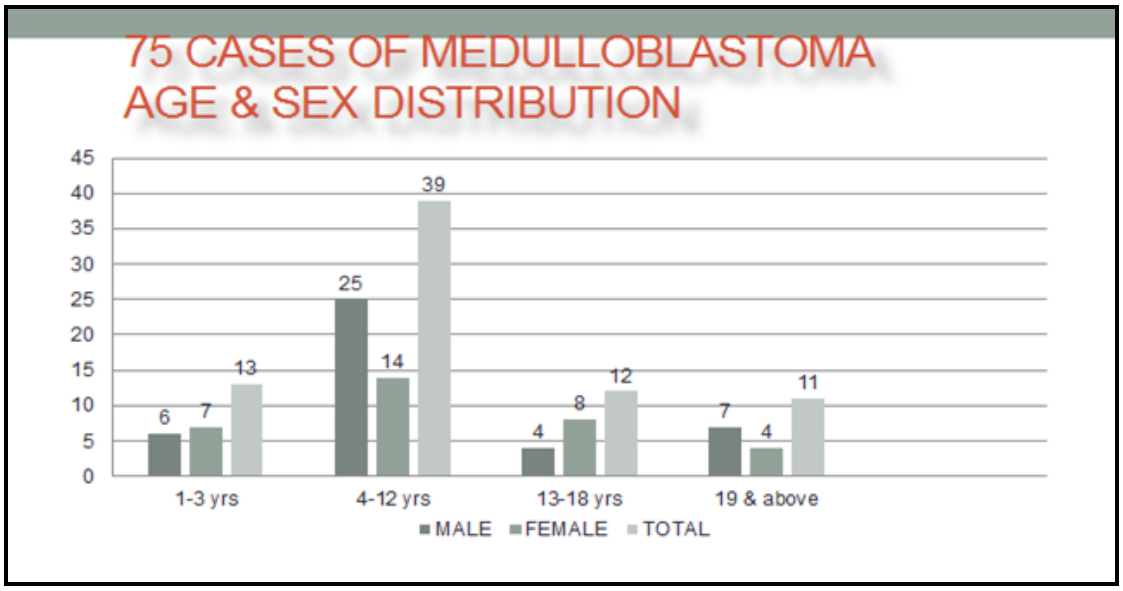
RESULTS

GENDER DISTRIBUTION

Among the 75 cases reported, males constitute 56% and females constitute 44%. i.e. total number of males treated was **42** and the total number of females treated was **33**.

Number of male treated during 2000-2010	Number of females treated during 2000-2010	Total persons treated during 2000-2010
42 (56%)	33(44%)	75(100%)

AGE WISE DISTRIBUTION



Total number of patients reported in the age group of 1-3 years, was 13. (6 male and 7 female). In 4-12 years of age, 39 cases were reported (25 male and 14 female). In 13- 18 years of age, 12 cases were reported (4 male and 8 female). Less than 19 years of age group, 11

cases were reported (7 male and 4 female). The total number of male was 42, and female was 33.

- ❖ The earliest age at presentation was 3 months (female baby).
- ❖ The maximum age at presentation was 35 years (1 male and 1 female)
- ❖ Maximum cases reported in " 4- 12 years " category (25 males and 14 females)
- ❖ Male : female ratio was 4: 3 (42 male : 33 female)

The distribution according to staging (CHANG STAGING)

Stage	Description	No of patients
M0	No evidence of subarachnoid metastasis	65 cases
M1	Tumor cells in CSF	3 cases
M2	Intracranial tumors beyond the primary site	5 cases
M3	Seeding in spinal subarachnoid space	1 case
M4	Extra neural spread	1 case

Chang staging is helpful to differentiate between the standard *risk* and the *high risk* patients. M0 is without any metastases; - in our study we have 65 cases in M0 stage. M1 stage is presence of tumor cells in CSF. It can be seen in MRI or by CSF cytology. We have 3 cases in M1 stage. M2 is having gross nodular seeding in cerebellar, cerebral subarachnoid space third and fourth ventricle, i.e. other than primary site intra cranially. We have 5 cases in M2 staging. M3 stage consists of

gross nodular seeding in spinal subarachnoid space, we have 1 case reported. M4 is extra neural metastasis. We have 1 case in M4 stage.

CLINICAL FEATURES

Symptoms of increased ICT

Headache	78%
Vomiting	73%
Diplopia	52%

Symptoms of Pressure Effect

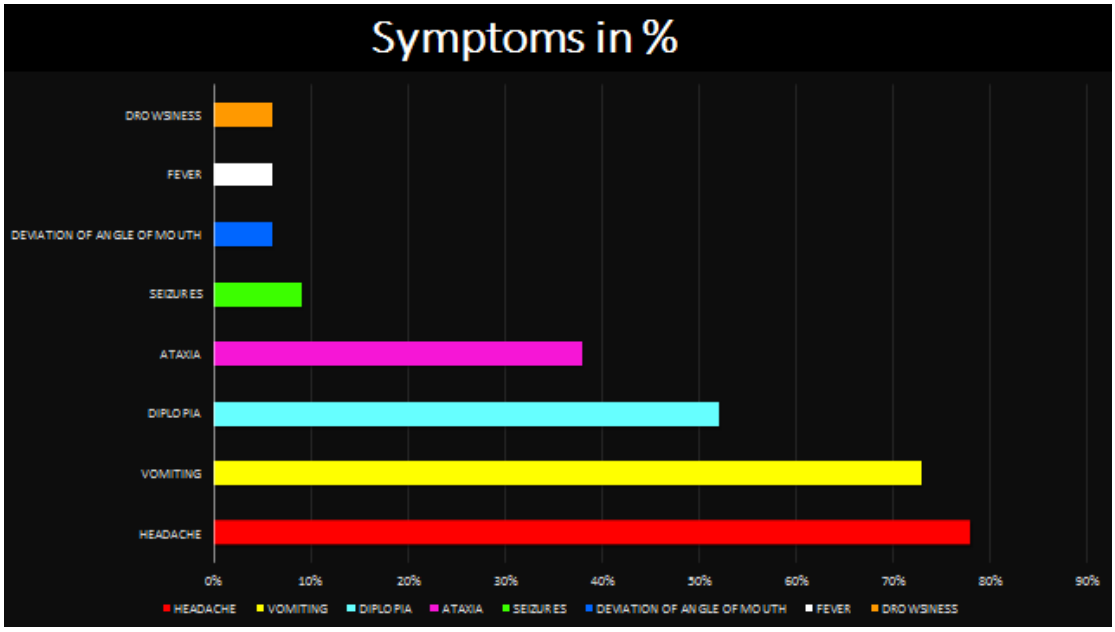
Ataxia	38%

Non Specific Presentations

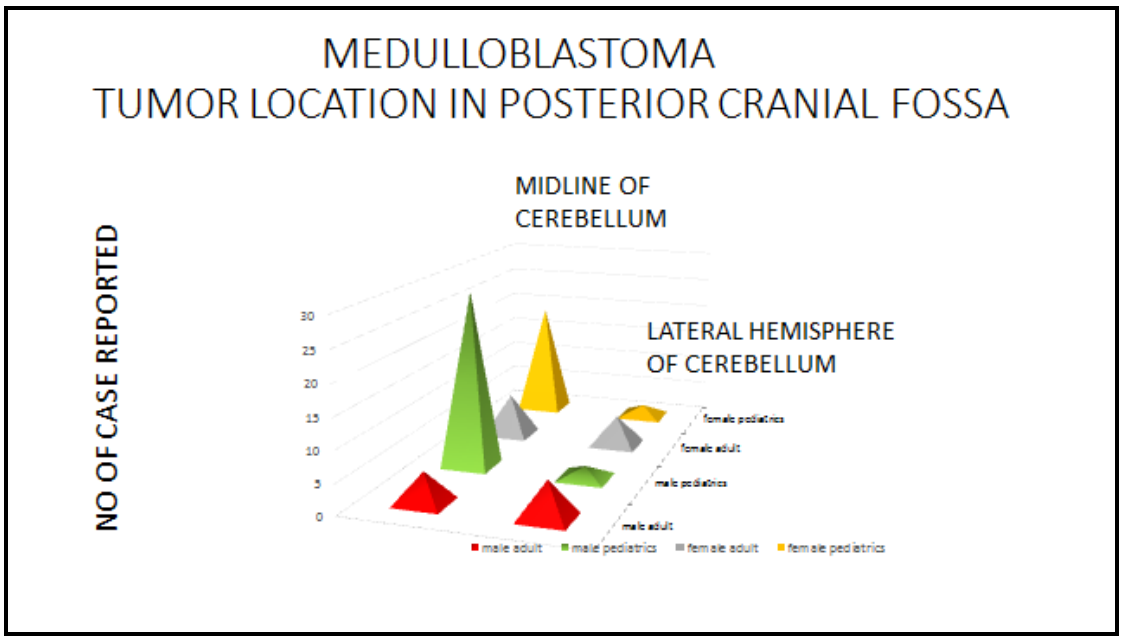
Deviation of angle of mouth	6.6%
Fever	6.6%
Drowsiness	6.6%
Involuntary micturition	2.6%
Weakness of limbs	2.6%
Tremors of hands	2.6 %
Nasal regurgitation	2.6%
Seizures	9.3%

Spectrum of clinical presentations is seen in medulloblastoma patients. The maximum number of patients presented with increased *intra cranial tension* features. **Head ache** is the commonest presentation (78%). Next comes **vomiting (73%)**, which relieves the headache. **Seizures** caused due to cerebral irritation in 9.3% of patients. Some

non-specific features also were present, deviation of angle of mouth due to 7 the nerve involvement, fever, drowsiness. They constitute 6.6% of clinical presentation. Involuntary micturition, weakness of limbs, tremors, nasal regurgitation were also present in 2.6%.



LOCATION OF THE TUMOR



Only 21% of cases are seen as lateral tumors(i.e)**15 patients** had lateral tumors. They were 4 cases (2 male; 2 female) of pediatric age group and 11 adult patients (6 males; 5 females).

Majority of tumors are seen in midline(81.3%). **60 patients** had midline tumors , situated in vermin of cerebellum or 4th ventricle. 48 patients (29 male;19 female)were in pediatric age group and 12 patients(5 male ;7 female) were adults.

LOCATION OF TUMORS – GENDER DISTRIBUTION

GENDER	MIDLINE TUMORS	LATERAL TUMORS	TOTAL	P VALUE
Male (%)	34 (81%)	8 (19%)	42(100%)	0.009
Female(%)	26 (81 %)	7(19%)	33(100%)	0.009
Total (%)	60 (81%)	15 (19%)	75(100%)	0.009

34 male have midline tumors and **8** male have lateral tumors. **26** females have midline tumors and **7** females have lateral tumors. Totally 60 midline tumors and 15 lateral tumors we encountered. The p value is significant. (Less than .05) In these 34 male of midline tumors, we have 29 pediatric cases and 5 adult cases. In 26 female cases 19 pediatric and 7 adult cases present. In lateral tumors 15 patients, we have 8 male, which contains 2 pediatric and 6 adult cases. In 7 female cases we have 2 pediatric and 5 adult cases.

	Centrally Located Tumors		Laterally Located Tumors	
Gender	**Male**	**Female**	**Male**	**Female**
Pediatric cases	29	19	2	2
Adult cases	5	7	6	5
Total	34	26	8	7

HISTOLOGICAL VARIENTS

Histologically we get 4 types. **Classica**l variety, **nodular** variety**, large cell** and **desmoplastic** varieties are most common group of histology. In classical histology we got 40 patients. They constitute the majority. In large cell/nodular histology, we get 13 patients. In desmoplastic type, we got 22 patients.

No	Type of histology	Number of occurrence
1	Classical	40 patients
2	Large cell/nodular	13 patients
3	Desmoplastic	22 patients

TREATMENT MODALITIES UNDERGONE

The standard care comprises of tri modality approach (with surgery, radiotherapy and chemotherapy). But 54% of the patients did not undergo all the three modalities. They have completed only partial treatment. Only 46% patients had completed all the three modalities of treatment.

Surgical excision of tumor And v-p shunt	only v-p shunt (no surgery)	Total candidates
65 (87%)	10 (13%)	75

In surgical category, 65 patients(87%) have undergone ventricular -peritoneal shunt along with subtotal / near total excision of intracranial tumor (34 male; 31 female) . 10 patients (13%) had undergone only ventricular -peritoneal shunt where no tumor excision was done. (8 male; 2 female).

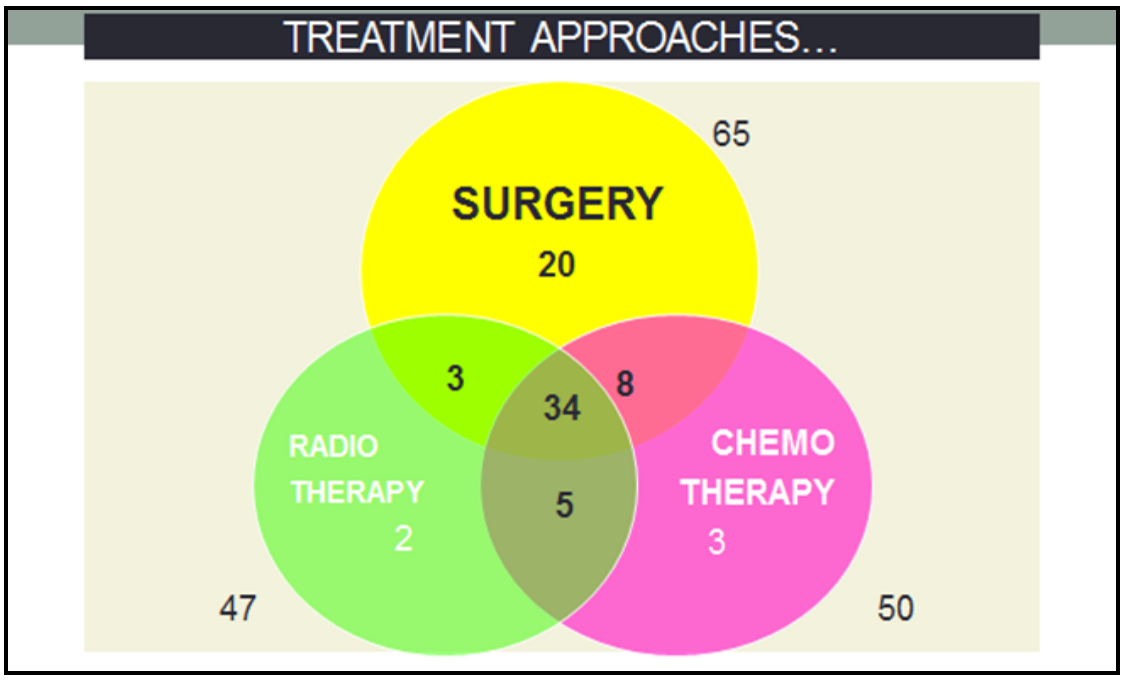
Total number of patients treated with Radiation was 47 (62.6%) out of which 27 were males and 20 were female. 28 patients were not given radiotherapy ,due to age less than 3 years and treatment default 15 male (35%) and 13 female (48.4%).

Radiotherapy	Male patients	Female patients	Total patient
Treated	27	20	47(62.6%)
Not treated	15	13	28(37.3%)

In radiotherapy arm, patients were given craniospinal irradiation for 36 gy followed by boost to posterior fossa up to 54 gyms. Cranium was treated by opposing lateral field. Spinal irradiation was given by single PA in two fields, separated by 1 cm distance. Field shifting was done in feather technique in upward direction.

In chemotherapy arm, 50 patients (66.6%) received chemotherapy (32 male and 18 female). Patients received weekly inj.vincristine (1.2 mg/m2) concurrently with radiation followed by adjuvant chemotherapy of PCV regimen once in 28 days for 6 cycle. (inj.cisplatin 75 mg/m2 IV day 1,inj.cyclophosphamide 1000 mg/m2 days 22, 23 and inj.vincristine 1.5 mg/m2 IV bolus max.2 mg days 2,8,15.) Weekly inj.vincristine is not given to adult patients since the toxicity symptoms are more. 25 patients (33.3%) didn't receive chemotherapy (10 male and 15 female)

Chemotherapy	Male	Female	Total
Given	32	18	50(66.6%)
Not given	10	15	25(33.3%)



This is the ven diagram showing the total treatment pattern. Total number of patients treated is 75. Surgery modality is "considered complete" if the patient has completed total **excision or near total excision.** Patient is considered as "surgically incomplete" if he has undergone just biopsy or subtotal excision. **65** patients have undergone total or near total surgery. Patients undergone only biopsy or subtotal excision is **10**.among the 65 cases that completed surgery, 20 patients didn't undergo any other modality. SURGERY ONLY completed patients are 20 in number(7 male + 13 female). 3 patients underwent radiotherapy also(Surgery+ radiotherapy= **3) 8** patients undergone chemotherapy in addition to surgery(surgery+ chemotherapy=8).

Number of patients given radiotherapy is **47**.Among them number of patients given only radiation is **2**.number of patients given

radiotherapy and chemotherapy is **5**.(radiotherapy+ chemotherapy=5) Number of patients given only chemo therapy is **3**. Number of patients given all the three treatment modality is **34**.

SINGLE MODALITY TREATMENT

25 cases out of 75 cases (33.33%) completed only one modality, surgery, radiotherapy or chemotherapy.

Only surgery completed : 7 male+ 13 female

Only chemotherapy : 3 male+ 0 female

Only radiotherapy given : 0 male+ 2 female

BI- MODALITY TREATMENT

16% of total cases completed double modality of treatment. They underwent surgery+ radiotherapy (or) radiotherapy + chemotherapy (or) surgery + chemotherapy.

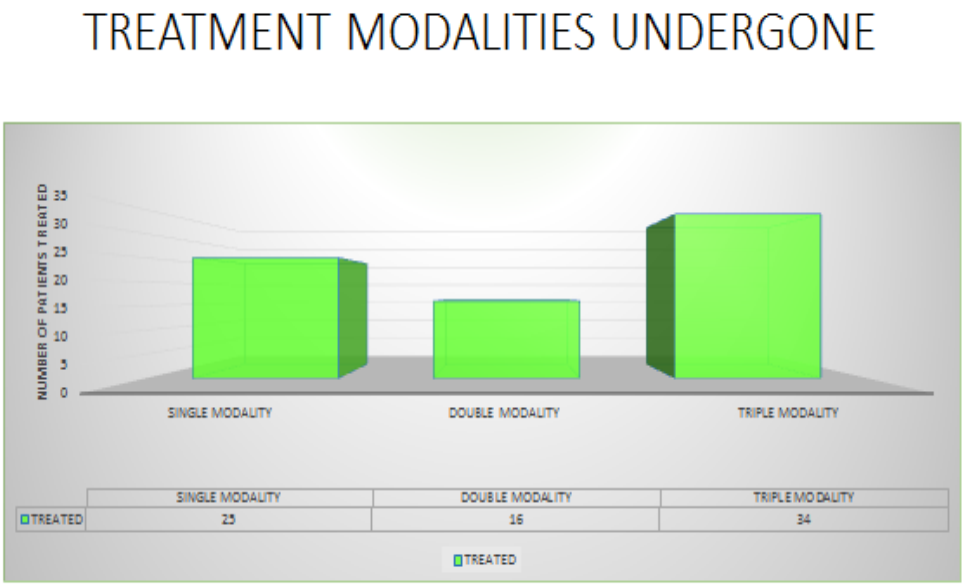
Surgery + chemotherapy completed : 5 males+ 3 female

Chemotherapy+ radiotherapy : 4 males+ 1 female

Surgery + radiotherapy : 3 male + 0 females

COMBINED TRI- MODALITIES TREATMENT

Only 45.3% of patients completed all the three modalities, 34 patients / 75 patients. = 20 males and 14 females.



Among the treatment modalities, 25 patients underwent only one type of treatment modality, (20- undergone surgery alone, 3 underwent chemo alone and 2 underwent radiotherapy alone.) 16 patients undergone bimodality approach, either surgery with chemo, or chemo with radiotherapy or radiotherapy and surgery. Only 34 underwent all the three modalities in right time.

Surgery, RT,chemotherapy	Male	female	Total
Single modality completed	10	15	25 (33.3%)
Bi modality completed	12	4	16 (21%)
All the three modalities completed	20	14	34 (45%)

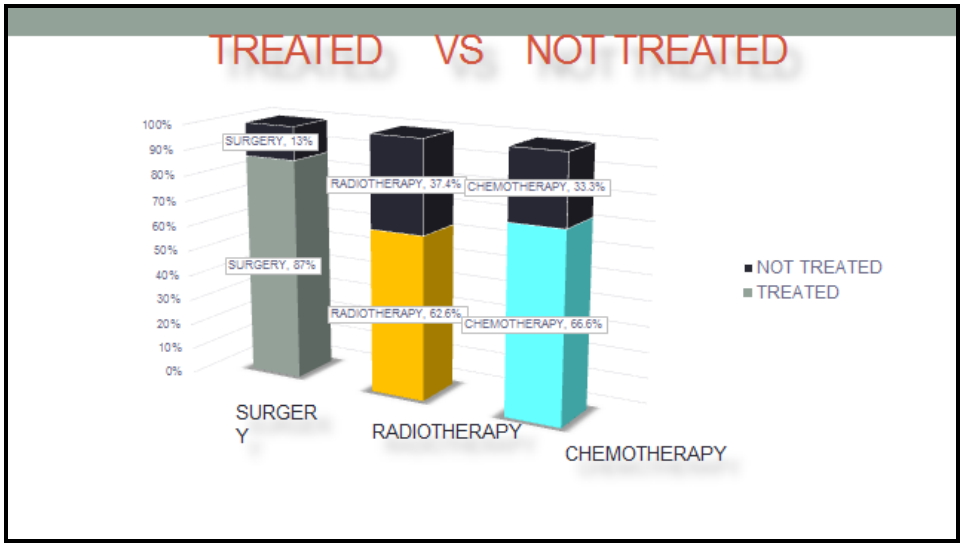
COMPILATION OF TREATMENT HISTORY

Treatment history				
No	Treatment history	Male (%)	Female(%)	Total patients(%)
1	No of patients **completed treatment**	**20/42** (47.61%)	**14** /33 (42.42%)	**34/75** (45.33%)
2	No of patients with **incomplete treatment**	**22/42** (52.38%)	**19/33** (57.57%)	**41/75** (54.66 %)

47% of male and 42.42 % of females completed the full treatment with maximum safe excision, radiotherapy and chemotherapy. They constitute 45% of total study group. 52% of male and 57 % of female undergone only partial treatment. They didn't undergo any one or two methods of treatment. They constitute 54.66%.

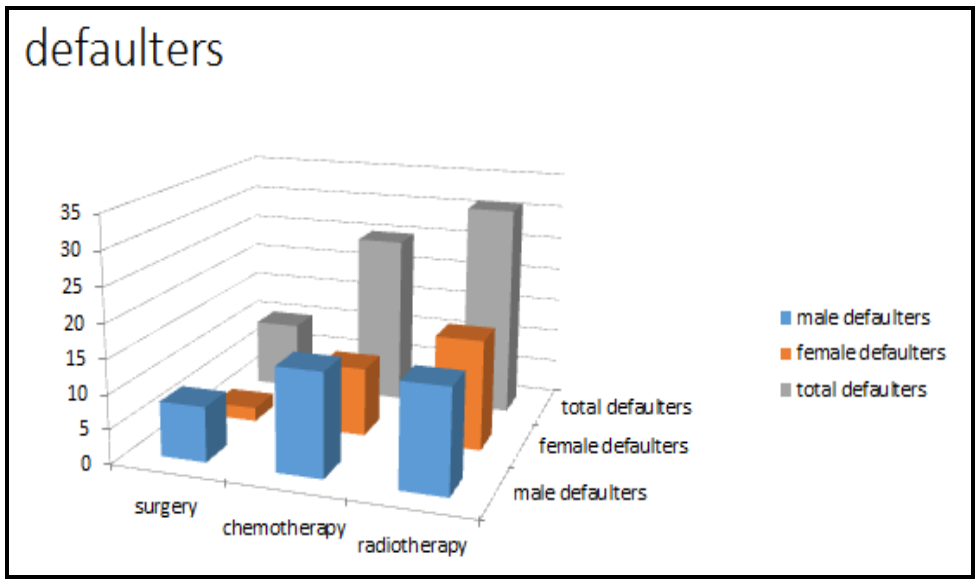
When we compare the percentage of *treatment completed* category, with percentage of those who *didn't complete the treatment*, the second one is more than the first one.

% of treatment completed patients < % of patients with incomplete treatment



DEFAULTERS

In individual arms among surgery, radiotherapy and chemotherapy, surgery is the arm in which highest % of patient's undergone treatment (87%). Only 13 % of patients were not operated. Radiotherapy arm has lowest enrollment of patients (62.6%). In radiotherapy arm 37.4% defaulters present. The chemotherapy arm has 66.6% of enrollment and 33 % defaulters.



REASON OF TREATMENT DEFAULT

1. Lack of awareness about different modalities that should be incorporated. Care givers fail to enlighten the patients regarding the treatment protocol and follow-up. (42%). " Lack of coordination among different treating surgeons and physicians" is one of the factors for patient's **lack of interest** in treatment. 56% of defaulters expressed that, they are not aware of the correct schedule of the treatment.

2. False belief of poor outcome of patient in the treatment (28%). Outright expressions of poor prognosis by the treating physicians sometimes force the patient and family members to default the treatment. It discouraged them to proceed with the treatment further.

3. Fear of toxicity during the treatment especially during chemotherapy and radiotherapy.

4. Lack of adequate follow up facility.

Establishment of a central monitoring committee among the different departments of treatment will ensure complete treatment in each individual without fear of drop out.

SURVIVAL RATES

SURVIVAL CURVE COMPARISIONS

1) Survival Between treatment completed group vs. incomplete treatment group.

2) Comparison between - survivals in single modality treatment

Vs.

-double modality survival

Vs.

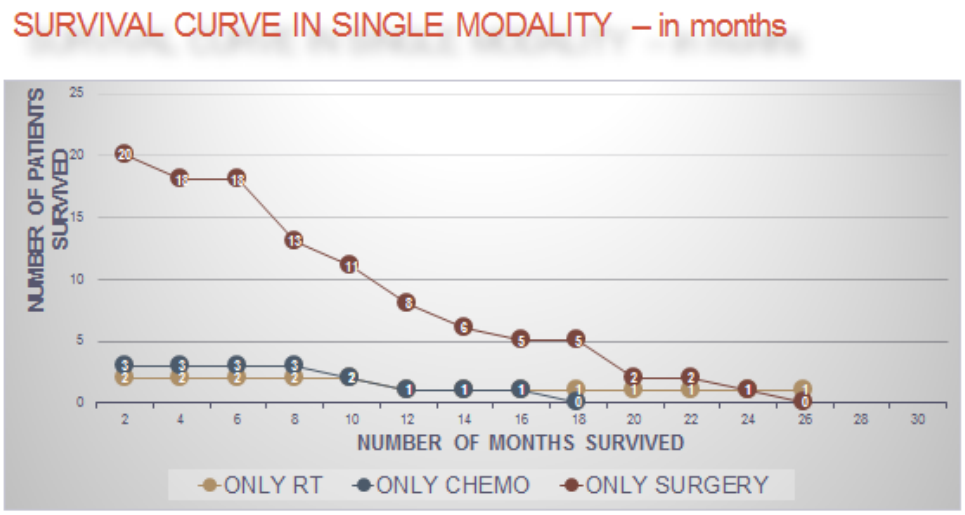
-survival of trimodality treatment approach

3) Survival comparisons between **adult** and **pediatric** patients.

4) Survival between **histological subtypes**.

5) Survival between patients having **centrally** located tumors and **laterally** located tumors.

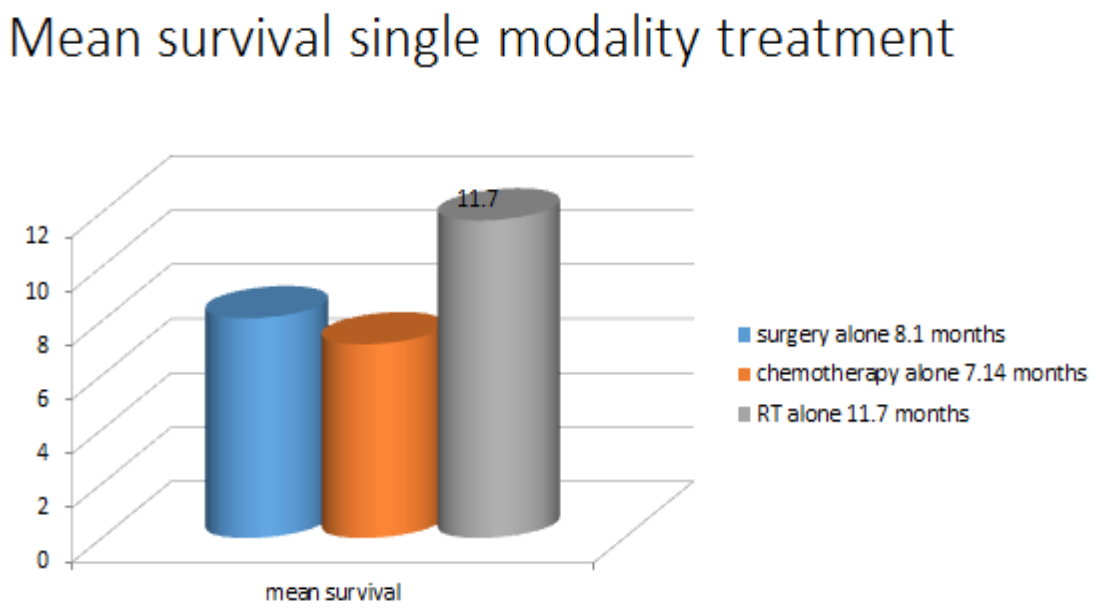
FOR SINGLE MODALITY TREATMENT COMPLITION



Those who completed only surgical modality of treatment (i.e., under gone excision of tumor) the survival maximum was 26 months**.** Minimum survival was 3 months. Mean survival was **8.1 month**. (7 male + 13 females). Only chemotherapy undergone patients, (3 males only) the maximum survival was 18 months. Minimum **survival** was 9 months. Mean survival was **7.14 months**. Only radiotherapy undergone patients, (2 females only) the maximum survival was 26 months. Minimal survival was 10 months. Mean survival was **11.7 months.**

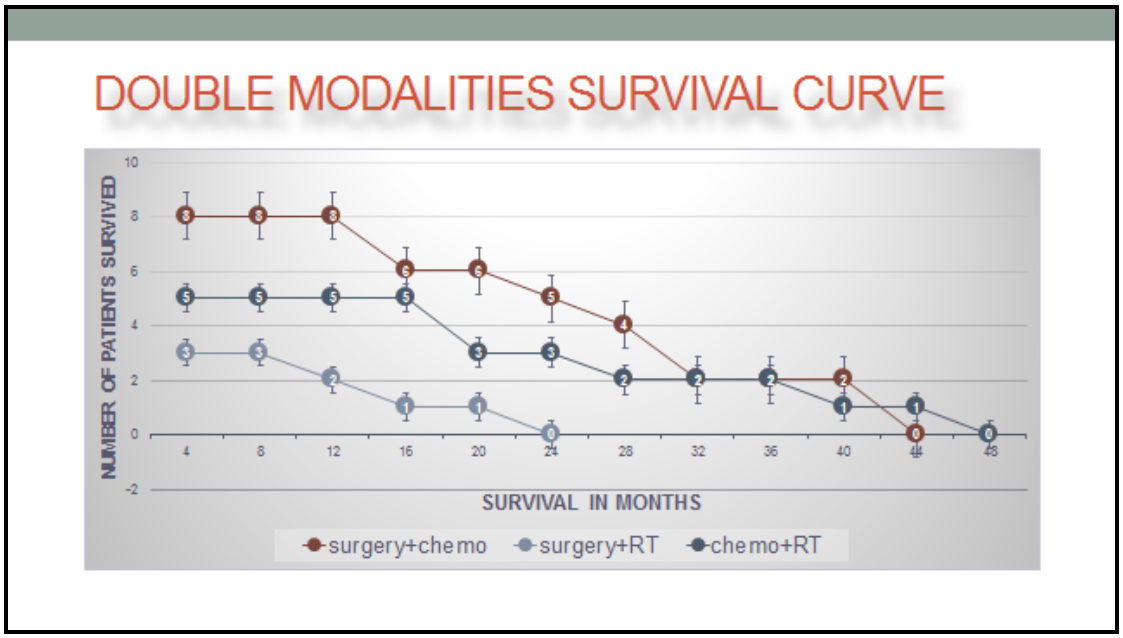
Treatment modality	Mean survival of life
Surgery alone	8.1 months
Chemotherapy alone	7.14 months
Radiotherapy alone	11.7 months

On the whole the mean survival for single modality approach is 8.27 months.



TWO MODALITY COMPLETED PATIENTS -SURVIVAL RATES

Maximum survival and minimum survival rates



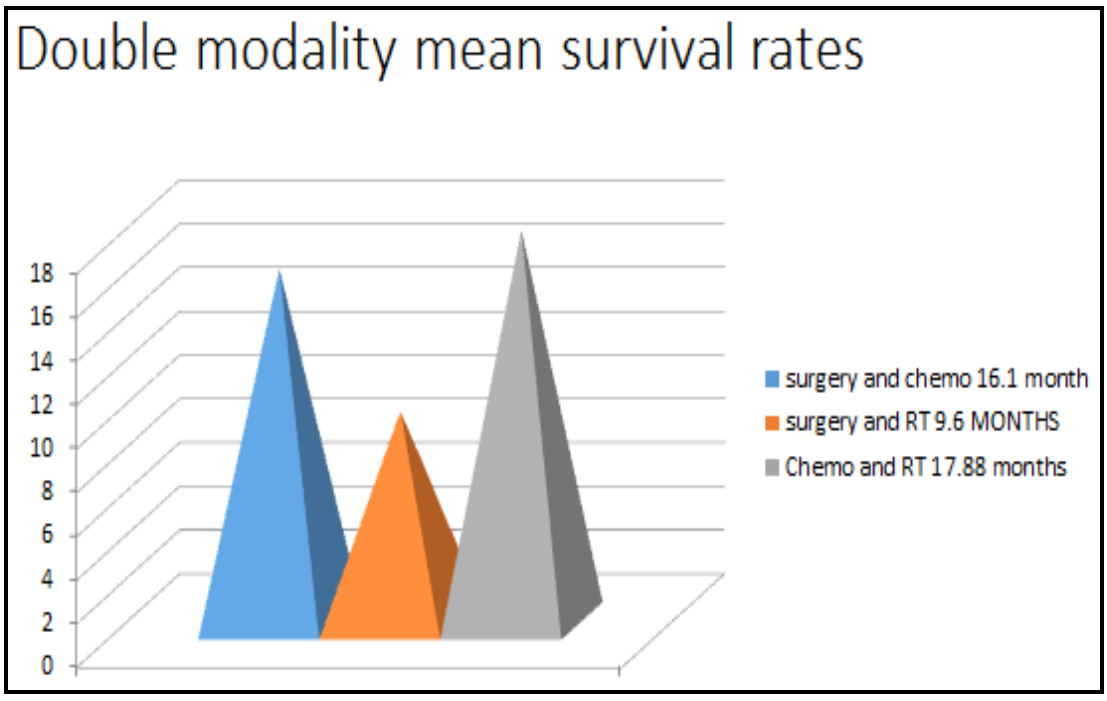
In patients who undergone surgery and chemotherapy (5 male and 3 female) the maximum survival was 40 months. Minimum survival was 12 months. Mean survival was **16.1 months.**

With surgery and radiotherapy (3 male only), the reported maximum survival was 20 months. Minimum survival reported was 8 months. Mean survival was **9.6 months**

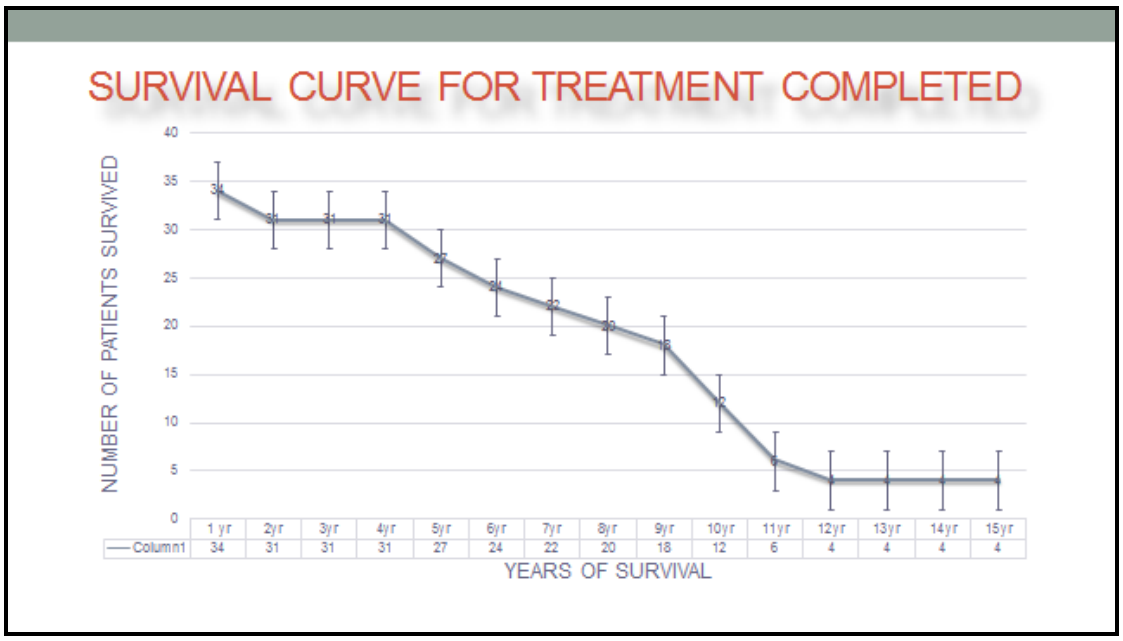
While radiotherapy and chemotherapy approach, (4 male and 1 female) gave maximum survival of 48 months, which was the highest survival among double modality treatment undergone patients. Minimum survival was 16 months, mean survival was **17.88 months.**

Treatments undergone	Mean survival rate
Surgery and chemo therapy	16.1 month
Surgery and radiotherapy	9.6 month
Radiotherapy and chemotherapy	17.88 months

As a whole the mean survival for bi modality approach is 15.43 months.



TREATMENT COMPLETED IN ALL 3 MODALITIES: SURVIVAL RATE



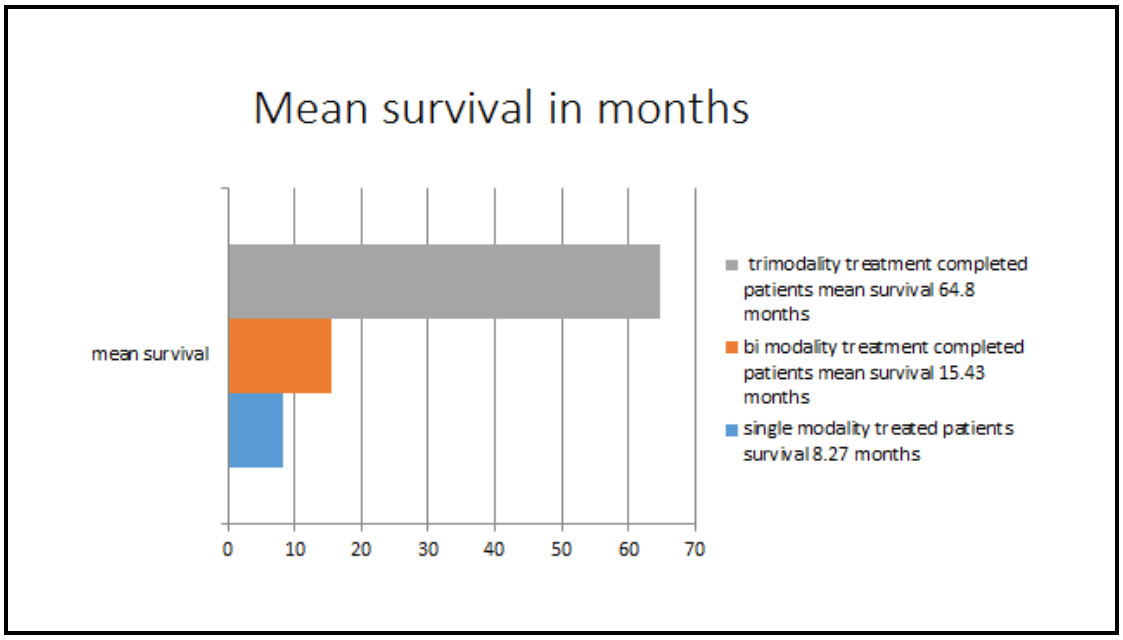
Here we can compare the survival rates of patients who completed treatment, and the survival of those with incomplete treatment.

Survival rates	Treated with surgery, chemo and RT	Incompletely treated patients
2 year survival	91.2% (31/34)	19.3%(6/ 41)
5 year survival	79.4% (27/34)	-
10 year survival	50 % (12/24)	
15 year survival	50 % (4/8)	-

The two year survival rate of treatment completed patients – 91.2% (31/34).The two year survival rate of incompletely treated patients – 19.3% (6/41). The 5 year survival of patients who completed treatment – 79.4% (27/34). The 5 year survival rate of patients treated

incompletely – 0% (none alive out of 41). The 10 year survival rate of patients who completed treatment- 50 % (12/24).

The mean survival comparison between single modality, bi - modality completed patients and tri -modality completed patient:

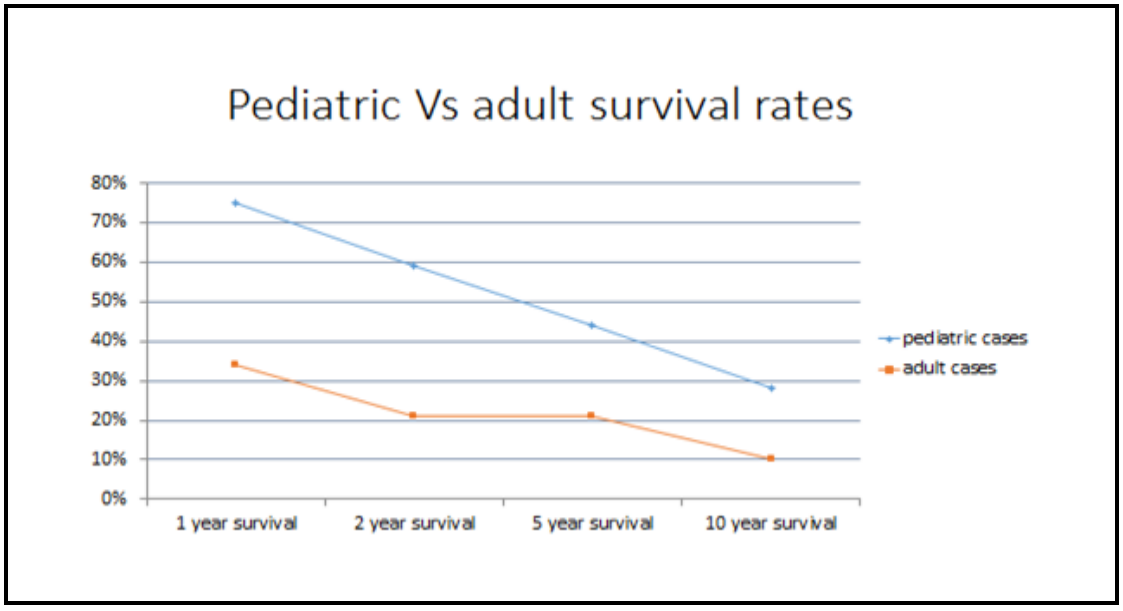


Total number of patients till 2008 was 58. Among those patients, total number of treatment completed patients was 24, who survived for 10 years. There is no 10 year survival rate for incompletely treated persons. During the year 2001- 2003 we have treatment completed list of patients, which comprises of 8 members out of 16 total members.Among these 8 persons, one person died during the year 2017. So the 15 year survival rate in treatment completed persons: 4/8 which is 50 % if complete treatment is given.

Pediatric Vs. adult medulloblastoma 2 yr., 5 yr. and 10 yr. survival rates:

We have totally 52 pediatric cases. It comprises of 31 male and 21 female**.** Age less than 3 years 13 patients, (6 male and 7 female). In the age group of 4 to 12 years we have 39 cases, (25 male patients and 14 females).

Survival rates	Pediatric cases	Adult cases
2 year survival	59%	21%
5 year survival	44%	21%
10 year survival	28%	10%



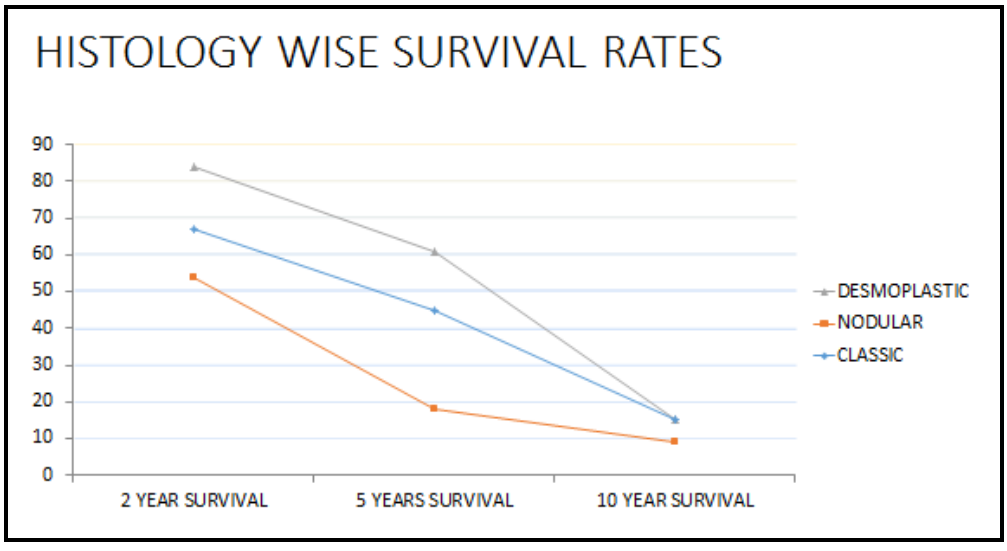
The survival rate was calculated among the pediatric cases, 2 year survival rate 59%, 5 years survival rate 44% and the 10 year survival rate 28%.

We have 23 cases in adult patients in study. (11 male and 12 female) the 2 year survival rate 21%, 5 years survival rate 21 %, 10 years survival rate 10%.

HISTOLOGICAL VARIANTS SURVIVAL RATES

We have 5 histological types of histological varieties. They are classic, desmoplastic, large cell,anaplastic and nodular . Among them, classical variant constitute more. The survival rates of these varieties are as follows: 2 year survival rate of nodular/large cell variety is 54%, 5 year survival tare is 18% and 10 year survival rate is 9%. Desmoplastic variant has better prognosis, 84% of 2 year survival rate, 5 year survival rate is 61% and 10 year survival rate is 45%. Classical histological variety has 2 years survival rate – 67%, 5 year survival rate – 45% and 10 years survival rate is 15%

Survival rates	Classical histology	Large cell/nodular	Desmoplastic variety
2 years survival	67%	54%	84%
5 year survival	45%	18%	61%
10 years survival	15%	9%	15%



In this chart, desmoplastic has highest 2 year and 5 year survival. 10 years survival becomes equal. Nodular/large cell variety has comparatively poor prognosis.

LATERALIZED TUMORS SURVIVAL RATES

Totally 15 patients were lateralized tumor patients, situated in cerebral hemispheres, pediatric cases 2 male and 2 female. Adult cases 11 cases 6 males and 5 females.

2 years survival rates: 8/ 15 = 53%. 5 year survival rates: 2/ 15 = 13%.

Survival rate	Number of cases	%
2year survival	8/ 15	53%
5 year survival	2/ 15	13%
10 year survival	0	0

MIDLINE TUMOR SURVIVAL RATES

We have 60 patients presented with midline tumors. The survival rates of those patients are 66% of 2 year survival rate, 41% 5 year survival rates, and 11% of 10 years survival rate.

Survival rates	Number of patients	Percentage
2 year survival	40/60	66%
5 year survival	25/ 60	41%
10 year survival	7/ 60	11%

RECURRANCE IN MEDULLOBLASTOMA PATIENTS

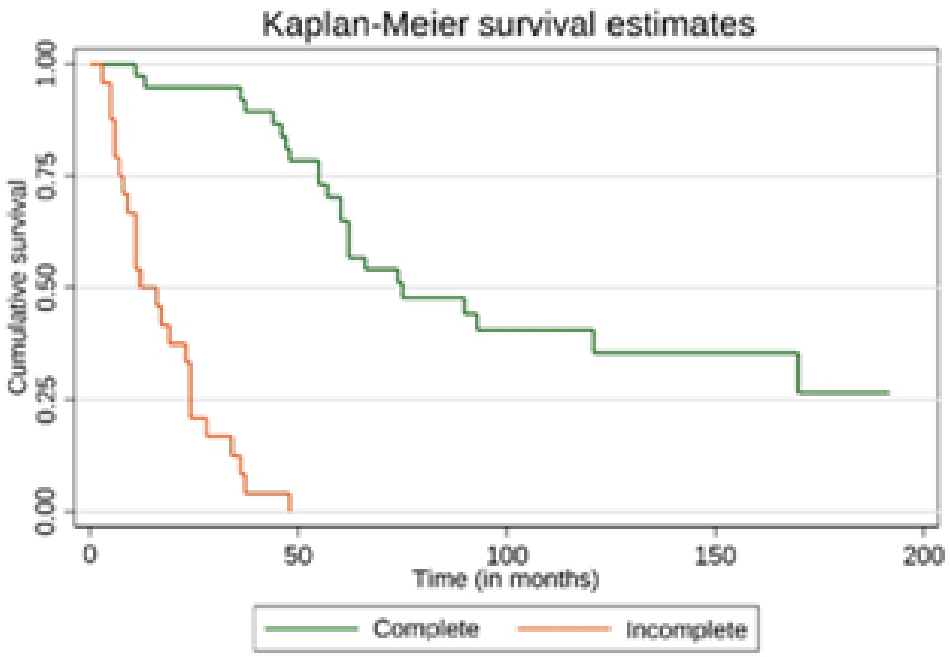
Out of total 75 patients, 7 had recurrence (3 loco regional and 4 distant recurrence) common features observed

- The period of recurrence ranges from 1- 9 years. Mean 4-5 years.
- Delay in adjuvant treatment following surgery/ incomplete treatment
- Local recurrence seen in posterior fossa 3_/ 7
- Distal recurrence seen in the body1)Bone and bone marrow indolent (mandible and spine metastasis) & viscera (hepatospenomegaly)
- Mostly in male (5:2) and in nodular variety

Age at presentation	Year of presentation	Year of recurrence	Site of recurrence	histology
7 year/ Female	2001	2005	Posterior fossa	classical
12 yr/ male	2001	2006	Posterior fossa	desmoplastic
19 yr / male	2004	2013	spine	nodular
25 yr/ female	2005	2006	hepato spleenomegaly	Nodular
12 yr/male	2008	2013	leptomeninges	classical
8 yr / male	2010	2015	Posterior fossa	nodular
10 yr / male	2010	2015	mandible	nodular

Treatment completed persons Vs incomplete treatment persons – survival rates

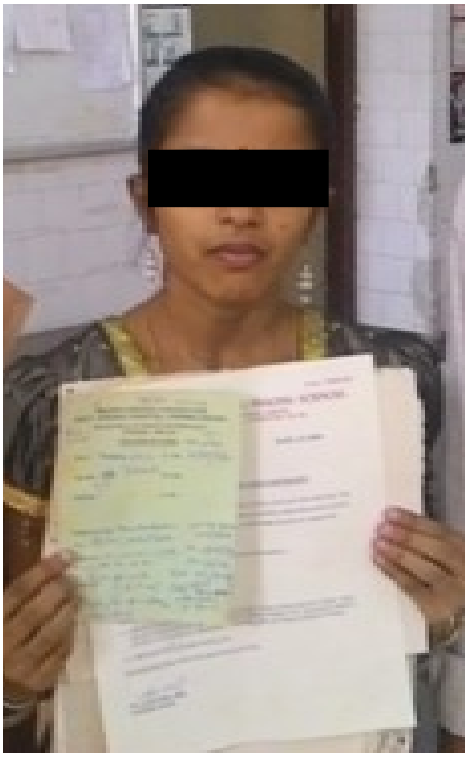
The mean age of the patients was 10.7 years with a S.D. of 7.3.



The median period of survival was 75 months (95% C.I.: 39, 111) in the complete group and 12 months (95% C.I.: 6, 18) in the incomplete group (Kaplan Meier, p-value<0.001). The Cox-proportional hazard model was used to determine the hazard ratio (HR) associated with incomplete treatment. The hazard associated with it was 18.8 (95% C.I.: 7.8, 46.1) as compared to those in the complete group.

QUALITY OF LIFE ASSESSMENT IN MEDULLOBLASTOMA SURVIVORS

Patients were assessed for their quality of life by asking simple questionnaire, QLQ – C30 version of EORTC.This questionnaire consisted of 30 simple questions in vernacular language, easily understandable. Totally 9 patients attended this questionnaire session in DEPARTMENTAL REVIEW, 5 patients were assessed in their home visit.



EORTC QLQ - C30 (version 3)

நாங்கள் உங்களைபும், உங்கள் ஆரோக்கியத்தைபும் பற்றி சில விஷயங்களை அறிய ஆர்வமாப் உள்ளோம். தயவு செப்து எல்லாக் கேள்விகளுக்கும் நீங்களே பதில் தாருங்கள். உங்களுக்கு உச்ச அளவில் பொருந்தும் எண்ணைச் சுற்றி வட்டமிடவும். "சரியான" அல்லது "தவறான" பதில்கள் கிடையாது. நீங்கள் தரும் விபரம் கண்டிப்பாக ரகசியமாக இருக்கும்.

தயவு செப்து உங்கள் பெயரின் முதல் எழுத்துகளை இட்டு நிரப்பவும். _____

உங்களது பிறந்த தேதி (நாள், மாதம், வருடம்) _____

இன்றைய தேதி _____

		இல்லவே இல்லை	ஒரு சிறிது	கணிசமாக	மிக அதிக அளவு
1	நீங்கள் ஒரு கனமான கடைச் சுமக்குப்பை அல்லது ஒரு லகப் பெட்டியைத் தூக்குவது போன்ற கடினமான வேலைகள் செய்கையில் ஏதாவது தொல்லை அனுபவிக்கிறீர்களா?	1	2	3	4
2	நீண்ட தூர நடை எடுக்கையில் நீங்கள் ஏதாவது தொல்லை கொண்டுள்ளீர்களா?	1	2	3	4
3	வீட்டுக்கு வெளியில் சின்ன நடை எடுக்கையில் நீங்கள் ஏதேனும் தொல்லை கொண்டுள்ளீர்களா?	1	2	3	4
4	பகலில் படுக்கை மீது அல்லது ஒரு நாற்காலியில் இருக்கும்படி நீங்கள் தேவையை உணர்கிறீர்களா?	1	2	3	4
5	நீங்கள் சாப்பிட, உடுத்த, குளிக்க அல்லது கழிப்பிடத்தைப் பயன்படுத்த உதவி தேவைப்படுகிறதா?	1	2	3	4
	கடந்த வாரத்தின் போது:				
6	நீங்கள் உங்கள் வேலையைபோ அல்லது மற்ற ஒவ்வொரு நாள் நடவடிக்கைகளைபோ செய்கையில் வரம்புக்குள்	1	2	3	4
7	நீங்கள் உங்களது பிடித்த பொழுது போக்குகள் அல்லது பிற ஓய்வு நேர நடவடிக்கைகளைத் தொடரும் போது வரம்புக்குள் இருந்தீர்களா?	1	2	3	4
8	நீங்கள் மூச்சுத் திணறலுடன் இருந்தீர்களா?	1	2	3	4
9	நீங்கள் உடலில் வலி கொண்டிருந்தீர்களா?	1	2	3	4
10	நீங்கள் ஓய்வு எடுக்கத் தேவைப்பட்டதா?	1	2	3	4
11	நீங்கள் தூங்குவதில் தொல்லை கொண்டிருந்தீர்களா?	1	2	3	4
12	நீங்கள் பலவீனமாக உணர்ந்து இருந்தீர்களா?	1	2	3	4

தயவு செப்து அடுத்த பக்கத்திற்குப் போகவும்.

	கடந்த வாரத்தின் போது:	இல்லவே இல்லை	ஒரு சிறிது	கணிசமாக	மிக அதிக அளவு
13	நீங்கள் பசியெடுப்பது இல்லாது இருந்தீர்களா?	1	2	3	4
14	நீங்கள் குமட்டுவது போல உணர்ந்தீர்களா?	1	2	3	4
15	நீங்கள் வாந்தியெடுத்துள்ளீர்களா?	1	2	3	4
16	நீங்கள் மலச்சிக்கல் கொண்டிருந்தீர்களா?	1	2	3	4
17	நீங்கள் தொடர்ந்து வயிற்றுப் போக்கு கொண்டிருந்தீர்களா?	1	2	3	4
18	நீங்கள் களைப்படைந்தீர்களா?	1	2	3	4
19	வலி உங்களது தினசரி நடவடிக்கைகளில் இடையூறு செய்ததா?	1	2	3	4
20	நீங்கள் ஒரு செய்தித்தாள் வாசிப்பது அல்லது தொலைக்காட்சி பார்ப்பது போன்ற விஷயங்கள் மேல் கவனம் செலுத்துவதில் கஷ்டம் கொண்டிருந்தீர்களா?	1	2	3	4
21	நீங்கள் பதற்றமான இறுக்கத்தை உணர்ந்தீர்களா?	1	2	3	4
22	நீங்கள் கவலைப்பட்டீர்களா?	1	2	3	4
23	நீங்கள் எரிச்சல் பட்டீர்களா?	1	2	3	4
24	நீங்கள் மன அழுத்தம் உணர்ந்தீர்களா?	1	2	3	4
25	நீங்கள் பொருட்களை ஞாபகம் கொள்வதில் கஷ்டப்பட்டிருந்தீர்களா?	1	2	3	4
26	உங்கள் உடல் நிலவரம் அல்லது மருத்துவச் சிகிச்சை உங்களது குடும்ப வாழ்க்கைபோடு குறுக்கிட்டுப் பாதித்து இருக்கிறதா?	1	2	3	4
27	உங்கள் உடல் நிலவரம் அல்லது மருத்துவச் சிகிச்சை உங்களது சமூக நடவடிக்கைகளோடு குறுக்கிட்டுப் பாதித்து இருக்கிறதா?	1	2	3	4
28	உங்கள் உடல் நிலவரம் அல்லது மருத்துவச் சிகிச்சை உங்களுக்கு நிதிக் கஷ்டங்களை உண்டாக்கி உள்ளதா?	1	2	3	4

பின்வரும் கேள்விகளுக்கு 1 லிருந்து 7 முடிய உ ள்ள எண்களில், உங்களது நிலவரத்திற்கு உச்ச அளவில் பொருந்தும் எண்ணைச் சுற்றி தயவு செய்து வட்டமிடவும்.

29 கடந்த வாரத்தின் போது, பொதுவாக, உங்களுடைய ஆரோக்கியத்தை நீங்கள் எவ்வாறு மதிப்பீடு செய்வீர்கள்?

1 2 3 4 5 6 7

(மிக மோசம்) (பிரமாதம்)

30 கடந்த வாரத்தின் போது, பொதுவாக, உங்களுடைய வாழ்க்கைத் தரத்தை நீங்கள் எவ்வாறு மதிப்பீடு செய்வீர்கள்?

1 2 3 4 5 6 7

(மிக மோசம்) (பிரமாதம்)

THE RESULTS OF ASSESSMENT:

1. During follow up 4 patients had short stature. Three patients have obesity. Patients had reported with significant alopecia, mainly occipital alopecia None of our patients had alopecia our patients did not have facial nerve palsy, strabismus, hearing impairment, hemi- and tetra paresis.

2. Almost all patients had significant deficits in neurocognitive functioning: Attention and processing speed were impaired in almost all patients, learning and memory impairments were present in 9 patients who are presently alive. No patients had language impairments or executivefunction impairments significant impairments in the overall level of intellectual functioning were seen in 10 patients.

3. Patients experienced significant problems in school, forcing them to discontinue the studies. Few patients attend regular schools, but needed remedial teaching. 3 patients were able to complete college education, but with low percentage of marks. Treated children though wish to participate in sports anplayful activities but unable to so because of fatigue and muscular weakness.

They are able to carry out activities of daily life, like bathing without others support. They experienced difficulty in walking for short distance (2 kilometers) and lifting articles weighing more than 5

kg. Few are able to carry out manual jobs like shops vendors Boys are doing shop assistant jobs, where they do normal physical activities.no one had Hearing impairment.

4) 7 persons had visual impairment. They needed refractory lenses for visual correction. No patient developed cataract.

5)90% of persons have aggressive behavior and irritable personality. They experience difficulty in having friendly relationship with others forcing them to be isolated among their peer group. Majority of patients experience emotional distress and physical discomfort during socializing. They wish to spend day time sleeping, even though nocturnal sleep disturbance are present.

6. Majority of them are not satisfied with their physical appearance. They feel they are shorter than their comparative age group. They display their displeasure towards physical beauty.

7. Majority of them experience difficulty in learning. They study lesser classes than their corresponding age group. They feel difficulty in understanding the lessons. Many discontinued their studies.

8. Majority of them don't want to disclose about their disease to friends and relatives. Many don't even want to give their photograph.

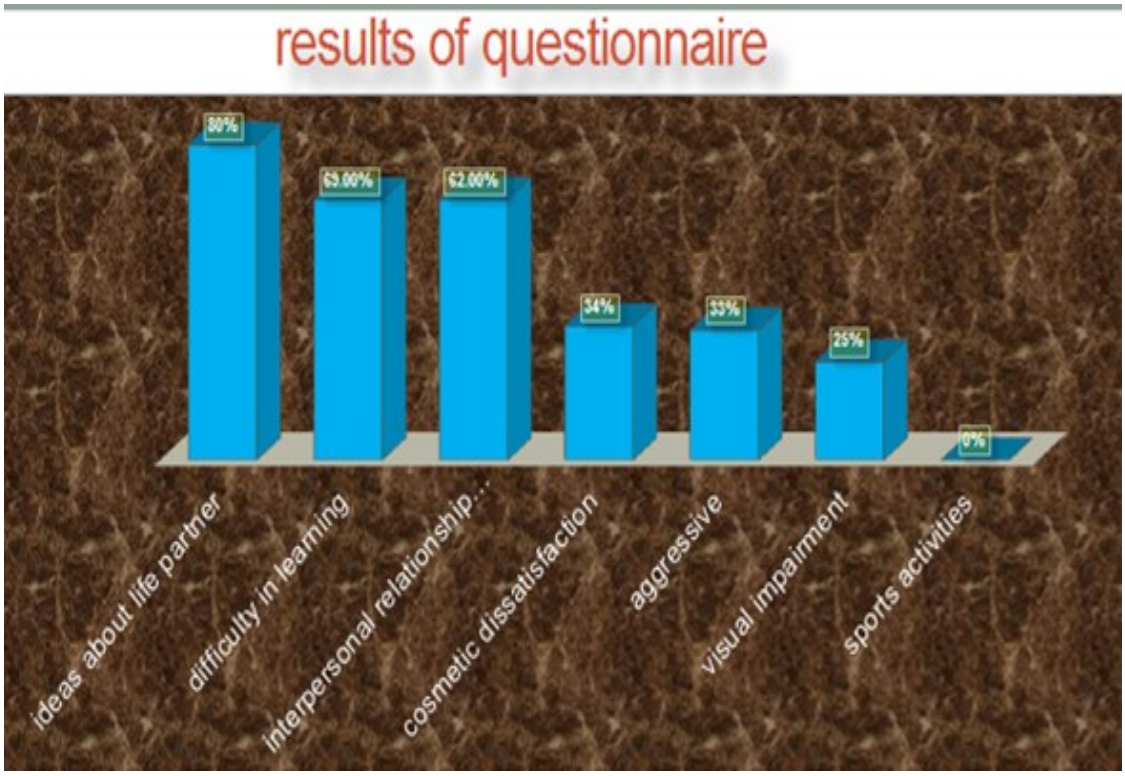
9. Bowel habits are often not normal, either constipation or irritable bloated abdomen present.They don't want to take treatment for any health issue for fear of experiencing pain.

10. Female patients are interested in family life with marriage. 66% of patients attained menarche. They have regular menstruation. There is a delay in secondary sexual characteristic appearance, like, axillary and pubic hair growth and breast development.

11. But majority of male patients consider the future married life as impossible. They have almost no moustache development. They are comparatively short. Majority don't want to get married. Majority grade their quality of life as poor.

12. The patients of medulloblastoma have the following late complications.

- Ideas about life partner- 80%
- Difficulty in learning-69%
- Interpersonal relationship-62%
- Cosmetic disfigurement-33%
- Aggressive nature, irritable –33%
- Visual impairment- 25%
- Sports activities -0%


results of questionnaire
80%
69.00%
62.00%
34%
33%
25%
0%
ideas about life partner
difficulty in learning
interpersonal relationship...
cosmetic dissatisfaction
aggressive
visual impairment
sports activities

DISCUSSION

It is clearly understandable , medulloblastoma is a notorious tumor arising from posterior fossa in vermin of cerebellum. The treatment of medulloblastoma has major challenges and yet remains a major frustration to the treating oncogist. Chennai is the capital city of Tamil and state, we have cases being referred from 7 districts from north Tamilnadu often.

From southern Tamilnadu, cases come to RGGGH radiation oncology department, by their own wish. Cases from Chengalpattu, thiruvannamalai, vilupuram, cuddalore, nagapattinam, perambalur and thiruvallur districts reach our hospital for oncological treatment. Our study starts from January 2000 to December 2010. The cases treated in oncological department of madras medical college, were taken for analysis.

The male: female ratio reported in this study is 4: 3. Total number of males treated was 42 and the total number of females treated was 33. There is no specific reason for the male preponderance. There is a theory of *loss of X chromosome* is told for Group 4 histology.

A significant expression of estrogen receptor beta, and no expression of estrogen receptor alpha, and low androgen receptors, found in medulloblastoma cell line, the tumor in female shows

differentiation, low Ki 67 and low p53 expression. This is proven in animal model, not in human. (53)

The earliest age at presentation was 3 months (female baby).In this age patient can be treated with surgery and chemo alone. We can postpone RT by managing the patient on chemo therapy. Infants if have larger primaries, the prognosis is very poor. They are poor candidates for intensive chemotherapy with high dose methotrexate / autologous stem cell transplantation; these patients are for complete resection only . sodium valproate can be used to keep away seizures in these babies.

Incidence was highest in patients aged 1-4 years at diagnosis, but patients aged 10-14 years showed increased incidence durig the year 2001- 2013.male showed increased incidence from 2000 to 2013 AS PER ONE STUDY(13) . In our study also it happens. In our study: Total number of patients reported in the age group of 1-3 years, was 13. (6 male and 7 female).

In 4-12 years of age, 39 cases were reported (25 male and 14 female). In 13- 18 years of age, 12 cases were reported (4 male and 8 female). Less than 19 years of age group, 11 cases were reported (7 male and 4 female). The total number of male was 42, and female was 33.

The maximum age at presentation was 35 years (1 male and 1 female). Usually adult has a favorable prognosis than pediatric age group. Usually adult has desmoplastic variety, in histological classification and WNT subtype in molecular classification. The only defect in adult is, we do not give weekly in vincristine, due to increased complication. In pediatric group, shh and group 3 are common.

Maximum cases reported in "4- 12 years "category (25 males and 14 females). There is a concept of *gonadotropin deficiency* following craniospinal irradiation in medulloblastoma; puberty will be in appropriate time in half of patients, whereas few patients can have delay in puberty. A study says complete or partial gonadotropin deficiency can be a consequence of craniospinal irradiation, if it goes beyond 60 gyms. (54)

Head ache is the commonest presentation (78%). Brain tumors as such cannot cause pain sensation, because brain is incapable of sensing pain. Brain has no pain receptors. Only when the tumor becomes larger and produce compression over nerves and vessels, they cause head ache. When the tumor causes compression over the CSF flow, it can increase intra cranial pressure, which can cause headache. Usually the tumor headache will be worsen in the morning, aggravated by coughing straining shouting, not manageable by pain killers.

Vomiting relieves the headache: vomiting is also a common symptom (73%). It is told, vomiting can be a first neurological sign of

brain tumors in children. Chronic vomiting may be due to increased intra cranial tension which leads to electrolyte imbalance. Tumor can because seizures caused due to cerebral irritation in 9.3%of patients. Some nonspecific features also present, deviation of angle of mouth due to 7 the nerve involvement, fever, drowsiness. They constitute 6.6% of clinical presentation. Involuntary micturition, weakness of limbs, tremors, nasal regurgitation also present in 2.6%.

Among the histological variants, large cell and anaplastic variants are notorious for unfavorable prognosis. Desmoplastic variant goes towards favorable prognosis. In adult 3 molecular types are seen mostly- SHH type (60-65%), Group D (20-25%), and WNT (10-15%).

Group C is almost exclusively present in pediatric and adolescent group. Germ line mutation of fused homolog (SUFU) causes sonic hedgehog medulloblastoma especially in first few years of life. This is much worse in prognosis, when compared with SHH medulloblastoma.

Transcriptional profiles of medulloblastoma tumors are done to identify the molecular subtype. If IHC for DKK1 is positive, it is WNT subtype. If IHC is positive for SFRP1, it is SHH subtype. If IHC is positive for NPR3, then it is group C. And if it is positive for KCNA1, it is group D. Group C has very less PFS. We didn't analyses the samples on the basis of molecular subtypes.

The distribution according to staging (CHANG STAGING)

Stage	Description	No of patients
M0	No evidence of subarachnoid metastasis	65 cases
M1	Tumor cells in CSF	3 cases
M2	Intracranial tumors beyond the primary site	5 cases
M3	Seeding in spinal subarachnoid space	1 case
M4	Extra neural spread	1 case

M0 is without any metastases, in our study we have 65 cases in M0 stage. M1 stage is presence of tumor cells in CSF. It can be seen in MRI or by CSF cytology. We have 3 cases in M1 stage. M2 is having gross nodular seeding in cerebellar, cerebral subarachnoid space third and fourth ventricle, i.e. other than primary site intra cranially. We have 5 cases in M2 staging. M3 stage consists of gross nodular seeding in spinal subarachnoid space, we have 1 case reported. M4 is extra neural metastasis. We have 1 case in M4 stage.

In adult medulloblastoma with leptomenigeal spread, pre radiation chemo therapy can increase the overall response and decrease the long term survival rates. The primary reason for treatment failure in medulloblastoma is the development of leptomeningeal metastasis. There are some methods to assess the seeding. MRI spine screening or CSF analysis can be done. It is said high levels of vascular endothelial cell growth factor and micro – RNA-210 are seen in medulloblastoma and its metastatic regions. Micro –RNA 210 can be analyzed by reverse

transcription quantitative polymerase chain reaction. VGFR m RNA can be assessed by western blot.in some instances, synchronous subarachnoid aneurysmal hemorrhage occurred in medulloblastoma patients at the site of metastasis. (It is very rare)

Tumor seeding is considered negative prognostic factor. The seedlings may be in spinal compartment, infra tentoria or supra tentoria compartments. Spinal compartment seeding patients have a long progression free survival (PFS). Their overall survival is also better. Majority of tumors are seen in midline (81.3%). We have 60 patients presented with midline tumors. The survival rates of those patients are 66% of 2 year survival rate, 41% 5 year survival rates, and 11% of 10 years survival rate.

MIDLINE TUMORS

Survival rates	Number of patients	Percentage
2 year survival	40/60	66%
5 year survival	25/ 60	41%
10 year survival	7/ 60	11%

Only 21% of cases are seen as lateral tumors. Totally 15 patients were lateralized tumor patients, situated in cerebral hemispheres, pediatric cases 2 male and 2 female. Adult can 11 cases- 6 males and 5 females.2 years survival rates: 8/ 15 (53%); 5 year survival rates: 2/ 15 (13%). Whereas for centrally located tumors, the survival rates are 2 year survival is 66%, 5 years survival rate is 41%, and 10 year survival

rate is 11%.Total number of cases of midline tumors are given in the table

Among medulloblastoma patients, there is a huge difference between the treatment completed arm and the incompletely treated arm. If the patient is treated with single arm his life expectancy would be around 7- 9 months. If he had completed two modalities the survival increases almost twice, around 16-18 months. In contrast to the previous two categories, the survival increases up to 64-66 months if he completes all 3 treatment modalities.

REASONS FOR NON-COMPLETION OF TREATMENT

1. Lack of awareness about different modalities that should be incorporate. Care givers fail to enlighten the patients regarding the treatment protocol and follow-up. (42%). Lack of coordination among different treating surgeons and physicians is one of the factors for patient's lack of interest in treatment. 56% of defaulters expressed that, they are not aware of the correct schedule of the treatment.

2. False belief of poor outcome of patient in the treatment (28%). Outright expressions of poor prognosis by the treating physicians sometimes force the patient and family members to default the treatment... It discouraged them to proceed with the treatment further.

3. Fear of toxicity during the treatment especially during chemotherapy and radiotherapy.

4. Lack of adequate follow up facility.

Establishment of a central monitoring committee among the different departments of treatment will ensure complete treatment in each individual without fear of drop out.

54% (52% male and 57% female) of the patients did not undergo all the three modalities.45% of patients completed full treatment. (47% male and 42.42 % female). When we compare the percentage of treatment *completed* category, with percentage of those who *didn't complete the treatment*, the second one is more than the first reason for not completing treatment.

Those who completed only surgical modality of treatment (i.e., under gone excision of tumor) mean survival was 8.1 month. Only chemotherapy undergone patients, Mean survival was 7.14 months .only radiotherapy undergone patients, mean survival was 11.7 months. Surgery and chemotherapy mean survival was 16.1 months. Radiotherapy and chemotherapy approach, mean survival was 17.88 months**.** The survival in those who completed all the three modalities, mean survival was 5.4 years. 5 year survival rate- 79.41 % (27/ 34) 10 year survival rate -35.29 % (12 / 34). The 15 year survival rate in treatment completed persons: 4/8 which is 50 % if complete treatment is given.

With surgery and radiotherapy mean survival was 9.6 month.

As per the study "Outcome of Medulloblastoma in Children: Long-Term Complications and Quality of Life Article in Neuropediatric June 2006 "

The mean follow-up time of all 51 patients following primary surgery was 6.6 years (range: 0.1 to 24.0 years). The 10-year overall survival was 53% and the 10-year progression-free survival was 40% as determined by the Kaplan-Meier method [26];. In our study, the follow up period ranges from 1 year to 17 years. Our study group is slightly larger. 75 patients. Our 2 year survival was 91-2%; 5 years survival 76.4% and 10 year survival 50%.44% patients had short stature. In our study we experienced short stature in 4 patients. Facial nerve palsy, strabismus, hearing impairment, visual impairment, hemi-and tetra paresis, present in their study, none of our patients have such cranial nerve palsy or hearing impairment. Visual impairment we had in 5 patients. Thirteen (72%) patients experienced significant problems in school.

90% of persons have aggressive behavior and irritable personality. They experience difficulty in having friendly relationship with others forcing them to be isolated among their peer group. Majority of patients experience emotional distress and physical discomfort during socializing. They wish to spend day time sleeping, even though

nocturnal sleep disturbance are present. Almost all patients had significant deficits in neurocognitive functioning:

Attention and processing speed were impaired in almost all patients, learning and memory impairments were present in 9 patients who are presently alive. No patients had language impairments or executive function impairments significant impairments in the overall level of intellectual functioning were seen In 10 patients.

Patients experienced significant problems in school, forcing them to discontinue the studies. Few patients attend regular schools, but needed remedial teaching. 3 patients were able to complete college education, but withlow percentage of marks.

The treated children though wish to participate in sports and playfulactivities but unable to so because of fatigue and muscular weakness. They are able tocarry out activities of daily life, like bathing without others support. They experienced difficulty in walking for short distance (2 kilometers) and lifting articles weighing more than 5 kg. Few are able to carry out manual jobs like shops vendors boys are doing shop assistant jobs, where they do normal physical activities.no one had hearing impairment.

7 persons had visual impairment. They needed refractory lenses for visual correction. No patient developed cataract. Majority of them

are not satisfied with their physical appearance. They feel they are shorter than their comparative age group. They display their displeasure towards physical beauty. Majority of them experience difficulty in learning.

They study lesser classed than their age group. They feel difficulty in understanding the lessons. Many discontinued their studies. Majority of them don't want to disclose about their disease to friends and relatives. Many don't even want to give their photograph.

Bowel habits are often not normal, either constipation or irritable bloated abdomen present They don't want to take treatment for any health issue for fear of experiencing pain Female patients are interested in family life with marriage. 69% of patients attained menarche. They have regular menstruation.

There is a delay in secondary sexual characteristic appearance, like, axillary and pubic hair growth and breast development. But majority of male patients consider the future married life as impossible. They have almost no moustache development. They are comparatively short. Majority don't want to get married. Majority grade their quality of life as poor.

CONCLUSION

Although medulloblastoma is a tumor of high mortality, correct treatment with surgery, chemotherapy and radiotherapy can save the life of the patient to certain extent. Surgical approach with total excision of the tumor along with ventriculoperitoneal shunt (wherever it is required) should be done to all the patients. Within 3 weeks patients must be given radiation to brain and spinal cord along with posterior fossa boost.Chemotherapy should be included in schedule.

The survival is better in pediatric age group, than the adults. Desmoplastic variant of histology carries very good prognosis, classical variant has average prognosis. Anaplastic and nodular variety has poorer prognosis. In this study no attempt was done to elicite the molecular varients of the tumors. Centrally located tumors carry better prognosis than the eccentrically located tumors. Prognosis depends on all these factors also.

Attenders must be instructed abiut the tri modality approach in the initial registration itself. Medulloblastoma special clinics must be created so that the patients are enrolled in the clinic and adequate treatment follow up is ensured. NGOs and voluntary organisations can be included in counselling the care takers about the disease prognosis and the correct line of management. Majority of the patients lost their

follow up. Some patients needed hormonal replacement, but they were not identified in time, so no hormone replacement was given.These issues can be easily solved by medulloblastoma clinics under an team of dedicated workers.

Although it is a notorious tumor for life, patient's attenders can be given a guarantee if the patient correctly undergoes the treatment schedule.

BIBLIOGRAPHY

1) http: // www.ncbi.nlm.nih.gov/pmc/articles/ PMC3167982/ small blue round cell tumors' am Podiatry Med Assoc. 2011 jul-aug ; 363-9, small blue round cell tumors.

2) pugh TJ ,weeratatne SD, Archer T C , Pomeranz krummel DA, Auchair D, Bochichio J, et al. medulloblastoma exome sequencing uncovers subtype specific somatic mutations. available: http//www.nature.com/nature/journal/ vaop/ nrecurent/ full/ 1329, html.

3) Survival and prognostic factors in pediatric patients with medulloblastoma in southern Thailand, Nalita N et al. J pediatr neurosci 2018 apr – jun

4) Survival of patients with adult medulloblastoma : A population based study Rose Lai et al. cancer 112 (7) , 1568-1574, 2008.

5) Survival and secondary tumors in children with medulloblastoma receiving radiotherapy and adjuvant chemotherapy : results of children s oncology group trial A 9961, Roger j packer, Tianni Zhou, Emi holmes, Neuro oncology 15 (1), 97- 103, 2012

6) Predicting intellectual outcomes among children treated with 35-40 Gy craniospinal irradiation for medulloblastoma, SL Palmer, A Gajjar, WE Reddick…2003- psychonet .apa.org

7) Effect of hypothalamic and pituitary irradiation on pubertal development in children with cranial tumors, RRappaport , R Brauner, P Czernichow, The journal of clinical endocrinology & metabolism 54 (6), 1164- 1168, 1982

8) The treatment and prognosis of medulloblastoma in children , a study of 82 verified cases, H.J.G BLOOM, WALLACE and J M HENK jan 1969,

9) Survival in padiatric medulloblastoma : a population based observational study to improve prognostication. Weil et al, Neuro Oncol,2017

10) A prospective study of progregression free and overall survival in pediatric medulloblastoma based on molecular subgroup classification. A single institutional study.

11) Incidence and survival trends for medulloblastoma in united states from 2001-2013. Khanna V et al. J Neuro oncol. 2017

12) Survival following tumor recurrence in children with medulloblastoma, D L Johnson et al. 2018.

13) Survival of very young children with medulloblastoma with treated with craniospinal irradiation , saran F H et al.Int Radiat oncol Biol phys. 1998

14) Medulloblastoma : recurrence and metastasis, Donya Aref; Sidney Croul, CNS Oncology , 2(4) 377-385, jul 2013.

15) Impact of site of tumor recurrence upon survival for children with recurrent or progressive medulloblastoma, Bowers DC et al, J Neuro surg . 2007

16) Incidence of medulloblastoma in Canadian children, Johnson DL et al. J Neuro oncol. 2014

17) Incidence of Gorlin syndrome in 173 consecutive cases of medulloblastoma, Evans DG , et al, Br J Cancer 1991

18) A gene for nevoid basal cell carcinoma syndrome acts as a tumor suppressor gene in medulloblastoma, Cowan R et al, 1997

19) Congenital anomalies and genetic syndromes in 173 cases of medulloblastoma, Evans G et al. Med Pediatric Oncol. 1993.

20) congenital icthyosis and medulloblastoma Walach N Dermatologica. 1977

21) Medulloblastoma in children and adolescents: a systemic reiew of contemporary phase 1 and 2 clinical trial and biological update

22) Medulloblastoma in childhood: an epidemiological study, farwell JR et al J Nuerosurg 1984

23) Quality of life for survivors children irradiated for brain tumor before the age of 4 years: jenkin et al . med pediatric oncol 1998

24) Quality of long term survival in young children with medulloblastoma, jonson et al. J Nuerosurg 1994

25) Brandes et al, long term results of prospective phase 2 trial of adult medulloblastoma:

26) Duffner et al. (1993) :

27) p9934 trial

28) COG ACN 0331 trial :Children oncology group- involved field RT and low dose craniospinal irradiation with chemotherapy in average risk medulloblastoma,

29) ACNS 0334 trial :for the treatment of newly diagnosed supratentoreal PNETs and high risk medulloblasoma children more than 3 years of age intensive induction chemotherapy with methotrexate followed by consolidation stem cell rescue

30) Neuropsychological sequel of the treatment of children with medulloblastoma , july 1996, Maureen dennis, Brenda j.spiegler, c.ross Hetherington

31) The perceived impact of cancer on quality of life for post treatment survivors of childhood cancer, brad j zebrack, wendy landier, march 11, 2011

32) Outcome of Medulloblastoma in Children: Long-Term Complications and Quality of Life Article in Neuropediatrics · June 2006

33) Treatment of early childhood medulloblastoma by postoperative chemotherapy and deferred radiothera py Stefan Rutkowski, Nicolas Ulrich Gerber,for the German Pediatric Brain Tumor group (S.R., N.U.G.,1

34) Louis DN OHGAKI h , Wiestler OD, cavenee WK , editors. WHO classification of tumors of central nervous system, Lyon: IARC ; (2007) 35. 36.MAGIC-medulloblastoma Advanced. Genomic international consortium stratifying and targeting pediatric medulloblastoma through genomics. Available : http// www. Bcgsc.ca/ project/ magic

35) Cho yj , tsherniak a, tamaya p, ligion a,gruelich et al, integrative genomic analysis of medulloblastoma identifies a molecular subgroup that drives poor clinical out come.

36) Nevoid basal syndrome LL Muzio.2008. http // orjd . biomed central.

37) Haberier c, slave i, czech t Gelpi, Heinkiz E,Budka H et al histopathological prognostic factors in medulloblastoma. High wxpression of surviving is related to unfavourabele outcome. Eur j cancer (2006). : 2993, 300310..

38) Quant imaging med surg.2017 feb ; 7(1), 169 posterior fossa syndrome a narravite review

39) Radiation to medulloblastoma adjusted to prevent recurrence to cribriform plate region Berta jereb, sita krishnaswami,ann reid, Jeffrey c allen cancer 54 (3), 602-604, 1984

40) Achenbach TM. Manual for the Child Behavior Checklist 4–18 and 1991 profile. Burlington, VT: University of Vermont, Department of Psychiatry, 1991

41) Achenbach TM. Manual for the Youth Self-Report and 1991 profile. Burlington, VT: University of Vermont, Department of Psychiatry, 1991

42) Ater JL, van Eys J, Woo SY, Moore B 3rd, Copeland DR, Bruner J. MOPP chemotherapy without irradiation as primary postsurgical therapy for brain tumors in infants and young children. J Neuro-Oncol 1997; 32: 243–252

43) Bradlyn AS, Ritchey AK, Harris CV, Moore IM, O'Brien RT et al. Quality of life research in pediatric oncology. Research methods and barriers. Cancer 1996; 78: 1333–1339

44) Calaminus G, Weinspach S, Teske C, Gobel U. Quality of life in children and adolescents with cancer. First results of an evaluation of 49 patients with the PEDQOL questionnaire. Klin Padiatr 2000; 212: 211– 215

45) Chapman CA, Waber DP, Bernstein JH, Pomeroy SL, LaVally B et al. Neurobehavioral and neurologic outcome in long term survivors of posterior fossa brain tumors: role of age and perioperative factors. J Child Neurol 1995; 10: 209–212

46) Chin HW, Maruyama Y. Age at treatment and long-term performance results in medulloblastoma. Cancer 1984; 53: 1952–1958

47) Dennis M, Spiegler BJ, Hetherington CR, Greenberg ML. Neuropsychological sequelae of the treatment of children with medulloblastoma. J Neuro-Oncol 1996; 29: 91–101

48) Duffner PK, Cohen ME, Thomas P. Late effects of treatment on the intelligence of children with posterior fossa tumors. Cancer 1983; 51: 233–237

49) Duffner PK, Horowitz ME, Krischer JP, Friedman HS, Burger PC et al. Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors. New Engl J Med 1993; 328: 1725–1731

50) Eiser C, Morse R. The measurement of quality of life in children: past and future perspectives. J Dev Behav Pediatr 2001; 2: 248–256

51) Felder-Puig R, Frey E, Proksch K, Varni JW, Gadner H, Topf R. Validation of the German version of the Pediatric Quality of Life Inventory

52) P13 K pathway regulates the survival of cancer stem cells residing in perivascular niche following radiation in medulloblastoma in vivo. D hamberdzumyan oj becher genes 2008 genesdev . cshlp.org

53) Gender effect in experimental models of human medulloblastoma: does the ER resceptor beta signelling pathway has a role? Javier s castresana,journal llist plos v (97) 2014,pmc 4804991

54) Gonadal dysfunction after treatment of intracranial tumors, e a livesey and C G D brook endocrine unit , middle sex hospital, London 1988.

INFORMATION TO PARTICIPANTS

Title: **"OBSERVATIONAL STUDY OF MEDULLOBLASTOMA IN BARNARD INSTITUTE OF RADIATION ONCOLOGY FROM 2001 TO 2010"**

Name of Participant:
Name of the Principal(co – investigator) : T. BHARATHI
Name of the institution : Department of radiotherapy, RGGGH, MMC.

You are invited to take part in this research/ study/procedures/tests. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

What is the purpose of research?

Medulloblastoma is a highly invasive , malignant , embryonal tumor of brain mostly from the posterior fossa. Its aggressive nature ,infiltrative character and tendency to systemic and leptomeningeal dissemination creates the need for combined modality therapy with surgery , radiotherapy and chemotherapy. After completing all such modalities, to assess the 2 yr, 5 yr, 10 yr & 15 yr survival of the patients this study is conducted.to assess the quality of life in living patients , this study is done. We have obtained permission from the Institutional Ethics Committee.

The study design

Retrospective study with available clinical records and patients follow up.

Study Procedure

U will be given a questionnaire with simple questions to assess ur mental and physical health.

You may have to come to the hospital (study site) for examination and investigations apart from your scheduled visits, if required.

Possible benefits to other people

The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history).

By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, Institutional Ethics Committee and any person or agency required by law like the Drug Controller General of India to view your data, if required.

The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. You will be taken care of and you will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment/discontinuing of procedures etc.

Signature of Investigator — Signature of Participant

Date — Date

INFORMED CONSENT FORM

TITLE OF THE STUDY **"OBSERVATIONAL STUDY OF MEDULLOBLASTOMA IN BARNARD INSTITUTE OF RADIATION ONCOLOGY FROM 2001 TO 2010"**

NAME OF THE PARTICIPANT:

NAME OF THE PRINCIPAL (Co – Investigator) :

NAME OF THE INSTITUTION: MADRAS MEDICAL COLLEGE

_____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in "OBSERVATIONAL STUDY OF MEDULLOBLASTOMA IN BARNARD INSTITUTE OF RADIATION ONCOLOGY FROM 2001 TO 2010"

1. I have read and understood this consent form and the information provided to me.

2. I have had the consent document explained to me.

3. I have been explained about the nature of the study.

4. I have been explained about my rights and responsibilities by the investigator.

5. I have been informed the investigator of all the treatments I am taking or have taken in the past 12 months including any native (alternative) treatment.

6. I have been advised about the risks associated with my participation in this study.*****

7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms. *****

8. I have not participated in any research study within the past 12month(s). *****

9. I agree to under go complete blood count, renal and liver function test, chest x ray, CT scan of the head and neck

10. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital. *****

11. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent. *****

12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.

13. I have understand that my identity will be kept confidential if my data are publicly presented

14. I have had my questions answered to my satisfaction.

15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document

Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

Name _____ Signature_____ Date_____
Name and Signature of impartial witness (required for illiterate patients):
Name _____ Signature_____ Date_____
Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent
Name _____ Signature_____ Date_____

ஆராய்ச்சி தகவல் தாள்

ஆராய்ச்சியின் பெயர்

மெடுல்லோபிளாஸ்டோமா- மூளைக்கட்டி புற்றுநோய்க்கு பூரண சிகிச்சை செய்த பிறகு அவர்களின் வாழ்க்கையின் தரம் எவ்விதமுள்ளது என்பதனை வினாத்தாள் மூலம் அறிதல்

ஆராய்ச்சியாளர் பெயர் :

பங்கேற்பாளர் பெயர் :

சென்னை ராஜீவ் காந்தி அரசு பொது மருத்துவமனைக்கு வரும் மூளைக்கட்டி நோயாளிகளுக்கு அறுவை சிகிச்சை, மருந்து சிகிச்சை மற்றும் கதிர்வீச்சு சிகிச்சை அளிக்கப்படுகிறது. அவ்விதம் சிகிச்சை பூரணமாக நிறைவுபெற்று பல நோயாளிகள் சென்றுள்ளனர். அவர்களில் 2001 முதல் 2010 வரை சிகிச்சை பெற்றவர்களில், உயிருடன் உள்ளவர்களிடம் அவர்களின் வாழ்க்கையின் தரம் பற்றி ஆராய்வது இந்த ஆராய்ச்சியின் நோக்கம்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க விரும்புகிறோம். இந்த ஆராய்ச்சியில் WHO சுகாதாரம் பற்றிய கேள்விகள் தழுவிய வினாத்தாள் அளிக்கப்படும். அதனால் தங்களின் நோயின் ஆய்வறிக்கையோ சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதை தெரிவித்துக்கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனையின் முடிவுகளையும் நோயின் தன்மை பற்றியும் ஆராய்ச்சியின் முடிவில் அறிவிப்போம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நாள் :
இடம் :

S. No	NAME	Admission	AGE	SEX	compltion	SURGERY	CHEMO	RT	MIDLINE\ LATERAL	histology	15	recurrence in 2004	DEATH	Chang
1	INDHUMATHI	2001	7	2	1	1	1	1	1	cl	5	RECUR 2005	2006	
2	PRIYANKA	2001	13	2		0	0	1	1	n	2		24 months	
3	BHAVANI	2001	9	2		1	1	0	1	cl	2			
4	**RAMESH**	2001	20	1	K	1	1	1	2	des	15			
5	**DIVYA**	2001	10	2	2	1	1	1	1	n	15			
6	LAVANYA	2001	4	2	3	1	1	1	1	cl	15			
7	CHANDRU	2001	12	1	K	1	1	1	1	des	5	recurrence,	2006	
8	BOOPALAN	2002	14	1	K	1	1	1	1	cl	4			M2
9	SENTHIL	2002	15	1		0	1	1	2	des	3			
10	SUNIL	2002	2	1		0	1	0	1	n	1		11 months	M2
11	NISHA	2002	11	2		0	1	1	1	n	5			
12	**KALAIVANAN**	2002	10	1	K	1	1	1	1	cl	15			
13	KARPAGAVALLI	2002	16	2		1	0	0	2	n	3			
14	SURYA	2002	2	1		1	0	0	1	cl	1	died during radiotherapy		M4
15	VINOTH KUMAR	2003	10	1		1	0	1	1	cl	1		2004	
16	DIVYA	2003	11	2	4	1	1	1	1	cl	0			
17	LOGESH	2004	7	1		1	0	1	1	cl	2			
18	BASHEER AHMED	2004	19	1	K	1	1	1	2	n	10	recurrence	spinemets	
19	BAGYALAKSHMI	2004	17	2	5	1	1	1	1	des	5			
20	SUBASREE	2004	13	2		0	0	1	2	cl	2		13 months	M2
21	**TAMARAI SELVI**	2004	6	2	6	1	1	1	1	cl	10			
22	DAYAKARAN	2004	4	1		1	0	1	1	cl	2			
23	ELUMALAI	2004	24	1		0	1	1	2	des	4			
24	MOHAMMED BASHA	2004	12	1	K	1	1	1	1	cl	6			
25	GANESH	2004	11	1		1	1	0	1	cl	2		34 months	M2
26	GOPI	2004	13	1	K	1	1	1	1	cl	2			
27	MOHANRAJ	2004	11	1	K	1	1	1	1	cl	3			
28	RAJESWARI	2004	20	2		1	0	0	2	n	1			
29	PRADEEP	2005	10	1	K	1	1	1	1	cl	10			
30	ARULMOZHI	2005	4	1		0	1	1	1	cl	1			
31	POORANI	2005	13	2		1	0	0	1	n	0			
32	KALEEWARI	2005	25	2		1	0	0	2	n	0	drop mets d2-d12	9 months	M3
33	RAJA RAGUVARAN	2005	6	1		1	0	0	2	cl	0			
34	SIVARAM	2005	3	1		1	1	0	1	cl	0			

S. No	NAME	Admission	AGE	SEX	compltion	SURGERY	CHEMO	RT	MIDLINE\ LATERAL	histology	15	recurrence in 2004	DEATH	Chang
35	JAYAVEL	2005	24	1		1	0	0	2	n	0			
36	SONIA	2005	2	2		1	0	0	1	n	0			
37	pavithra	2005	8	2	7	1	1	1	2	cl	0		died during 7th#	M2
38	**PAVUN**	2005	14	2	8	1	1	1	1	des	10			
39	MRIDULA	2006	2	2		1	0	0	1	n	0			
40	DINESH	2006	11	1		1	0	1	1	n	2			
41	**BALAJI**	2006	8	1	K	1	1	1	1	cl	10			
42	MOHAMMED SALEEM	2007	5	1		1	0	0	1	cl	5			
43	ZENPUTRET	2007	2	2		1	0	0	1	n	0			
44	KIRAN	2007	10	1	K	1	1	1	1	n	2			
45	**RAMMOHAN**	2007	11	1	K	1	1	1	1	des	5			
46	VANITHA	2007	6	2	9	1	1	1	1	cl	5			
47	aswin	2008	13	1		0	1	0	1	n	0		9 months	
48	ASIF	2008	2	1		1	1	0	1	n	2	rt deferred		
49	THANIGAMALAI	2008	12	1	K	1	1	1	1	cl	5	leptomeningeal dissemination for chemo		M3
50	**VIDYASRI**	2008	5	2	10	1	1	1	1	cl	5			
51	ARTHI	2008	25	2		1	0	0	2	des	0			
52	**INIYAVAN**	2008	6	1	K	1	1	1	1	cl	5			
53	VASANTHA KUMAR	2008	6	1		1	0	0	1	cl	0			
54	NAVYA	2008	2	2		1	0	0	1	cl	0			
55	BALAKRISHNAN	2008	1	1		0	1	0	1	cl	0		17 months	
56	**THEJA**	2008	5	2	11	1	1	1	2	cl	10			
57	SYED BASHA	2008	1	1		1	1	0	1	n	4			M1
58	VENNILA	2008	35	2		1	0	0	1	n	1		8 months	
59	PUGALENDI	2009	7	1	K	1	1	1	2	des	5			
60	RAJESWARI	2009	4	2	12	1	1	1	1	des	2			
61	THIRUNAVUKKARASU	2009	7	1	K	1	1	1	1	des	5			
62	SRINITHI	2009	2	2		1	1	0	1	cl	0			
63	SIVAKUMAR	2009	25	1		1	0	0	2	des	0			
64	NOUSHAD ALI	2009	27	1		1	0	0	1	n	3		7 months	M1
65	MALINI	2009	5	2		1	0	0	1	n	0		9 months	
66	ABIRAMI	2009	13	2		1	0	0	1	cl	3			
67	**MUTHUKANNAN**	2010	17	1	K	1	1	1	1	cl	5			
68	JEEVANANDA	2010	8	1		0	1	1	1	n	5	recurence		M1

S. No	NAME	Admission	AGE	SEX	compltion	SURGERY	CHEMO	RT	MIDLINE\ LATERAL	histology	15	recurrence in 2004	DEATH	Chang
69	**JEYALAKSHMI**	2010	12	2	13	1	1	1	1	cl	5			
70	MUTHURAMALINGAM	2010	10	1	K	1	1	1	1	cl	5	recurrence mandible		
71	THENMOZHI	2010	12	2	14	1	1	1	1	cl	5			
72	**HARIPRASAD**	2010	7	1	K	1	1	1	1	cl	5			
73	**SURENDRAN**	2010	12	1	K	1	1	1	1	des	5			
74	SWETHA	2010	2	2		1	0	0	1	n	0		3 months	
75	HEMAPRIYA	2010	2	2		1	1	0	1	n	0		23 months	

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301A
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.T. Bharathi
Post Graduate in M.D. Radio Therapy
Madras Medical College
Chennai

Dear Dr.T.Bharathi,

The Institutional Ethics Committee has considered your request and approved your study titled **"OBSERVATIONAL STUDY OF MEDULLOBLASTOMA IN BARNARD INSTITUTE OF RADIATION ONCOLOGY 2001-2010"**
NO. 19012017.

The following members of Ethics Committee were present in the meeting hold on **03.01.2017** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.M.K.Muralidharan,MS.,M.Ch.,Dean, MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.B.Vasanthi,MD., Prof.of Pharmacology.,MMC,Ch-3	: Member
5.Prof.A.Rajendran,MS, Prof. of Surgery,MMC,Ch-3	: Member
6.Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch	: Member
7.Prof.Baby Vasumathi,MD.,Director, Inst. of O & G	: Member
8.Prof.K.Ramadevi,MD.,Director,Inst.of Bio-Che,MMC,Ch-3	: Member
9.Prof.R.Padmavathy, MD, Director,Inst.of Pathology,MMC,Ch-3	: Member
10.Prof.S.Mayilvahanan,MD,Director, Inst. of Int.Med,MMC, Ch-3	: Member
11.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
12.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
13.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

Received a copy

Urkund Analysis Result

Analysed Document:	Observational study of medulloblastoma thesis typing.docx (D42612738)
Submitted:	10/16/2018 10:45:00 AM
Submitted By:	bharathithavasi@gmail.com
Significance:	4 %

Sources included in the report:

finalYearDissertation.docx (D30529538)
Lara Seric, Vetenskaplig rapport.pdf (D35596580)
http://tampub.uta.fi/handle/10024/66911
https://reference.medscape.com/article/987886-overview
http://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1130-14732011000600002
http://www.cancernetwork.com/pediatric-cancers/tale-two-tumors-pediatric-and-adult-medulloblastoma
https://www.stjude.org/disease/medulloblastoma.html
https://en.wikipedia.org/wiki/Medulloblastoma
https://plaza.umin.ac.jp/sawamura/pediattumor/medullo/
https://emedicine.medscape.com/article/1181219-treatment
https://link.springer.com/article/10.1007/s11060-017-2594-6

Instances where selected sources appear:

24